CLINICAL STUDY PROTOCOL

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY AND BIOMARKER EFFECTS OF ALZ-801 IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE AND APOE4/4 GENOTYPE

Short Title:	Phase 3 Study of ALZ-801 in APOE4/4 Early AD Subjects
Study Abbreviation:	APOLLOE4
Sponsor:	Alzheon, Inc. 111 Speen Street, Suite 306 Framingham, MA 01701 USA
Sponsor Medical Officer:	[redacted]
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Clinical Research Organization:	[redacted]
Sponsor Protocol No.:	ALZ-801-AD301
IND Number:	125760
EudraCT Number:	2020-005755-20
Study Drug Name	ALZ-801
Development Phase:	Phase 3
Date of Original Protocol:	24 DEC 2020
Amendment Number:	2
Date of Amendment 1:	09 FEB 2021
Date of Amendment 2:	24 JAN 2022
Version of Protocol:	3.0

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Declaration of Sponsor:

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy, Safety and Biomarker Effects of ALZ-801 in Subjects with Early Alzheimer's Disease and APOE4/4 Genotype

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP).

_____ _____

[redacted] Date

Chief Medical Officer
Alzheon, Inc.
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STATEMENT OF COMPLIANCE

Declaration of Principal Investigator:

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy, Safety and Biomarker Effects of AlZ-801 in Subjects with Early Alzheimer's Disease and APOE4/4 Genotype

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), in accordance with the study protocol, the current International Council for Harmonisation (ICH) Guideline for GCP, and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Principal Investigator

_____ _____

Name: Date
Title:
Institution:

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	Amyloid-β or beta amyloid peptide
AChEI	Acetyl cholinesterase inhibitors
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADAS-Cog 11	ADAS-Cog 11 items
ADAS-Cog 13	ADAS-Cog 13 items
AE	Adverse event
A-IADL	Amsterdam Instrumental Activities of Daily Living
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ALZ-801	Pro-drug of tramiprosate; tramiprosate conjugated to valine
ANCOVA	Analysis of covariance
APOE	Apolipoprotein E
APOE4	ε4 allele of apolipoprotein E gene
APOE4/4	Homozygosity for ε4 allele of apolipoprotein E gene
APOE4 carrier	Subject who is either heterozygous or homozygous for the ε4 allele of apolipoprotein E gene
aPTT	activated partial thromboplastin time
ARIA-E	Amyloid related imaging abnormalities with vasogenic edema
ARIA-H	Amyloid-related imaging abnormalities due to haemosiderin deposition
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
β	Beta
BACE	β-secretase or β-site amyloid precursor protein cleaving enzyme
BID	Twice per day
BMI	Body mass index
BP	Blood pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CAA	Cerebral amyloid angiopathy
CBD	Cannabidiol
CBL	Change from baseline
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating– Sum of Boxes
cGMP	current Good Manufacturing Practices
COVID-19	Coronavirus disease 2019
CP	Completer population
CRA	Clinical research associate
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
d	Day

Abbreviation	Definition
DAD	Disability Assessment for Dementia
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EDC	Electronic data capture
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
ET	Early termination
EU	European Union
FDG	Fluorodeoxyglucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFAP	Glial fibrillary acidic protein
GI	Gastrointestinal
GGT	γ-Glutamyl transferase
HbA1c	Glycosylated hemoglobin
hCG	human chorionic gonadotropin
HCV RNA	Hepatitis C virus RNA
Hep B S Ag	Hepatitis B surface antigen
Hep C Ab	Hepatitis C antibody
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LP	Lumbar puncture
LFT	Liver function test
MAD	Multiple ascending dose
MAO	Monoamine oxidase
MCI	Mild cognitive impairment
MCV	Mean corpuscular volume
MDD	Major depressive disorder
MDMA	3,4-Methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute(s)

Abbreviation	Definition
mITT	modified intent-to-treat
MMRM	Mixed effects model repeated measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NfL	Neurofilament light
NFT	Neurofibrillary tangles
NIA	National Institute on Aging
NIA-AA	National Institute on Aging-Alzheimer's Association
NPI	Neuropsychiatric Inventory
OC	Observed case
OHRP	Office of Human Research Protection
p-tau, P-tau	Phosphorylated tau
p-tau$_{181}$	Tau phosphorylated at threonine 181
p-tau$_{217}$	Tau phosphorylated at threonine 217
PET	Positron emission tomography
PK	Pharmacokinetic(s)
PPP	Per protocol population
PR interval	Time from the onset of the P wave to the start of the QRS complex
PT	Prothrombin time
QA	Quality assurance
QC	Quality control
QoL	Quality of life
QoL-AD	Quality of Life in Alzheimer's Disease
QRS duration	Interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization
QT interval	Interval representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT (interval)
QTcF	corrected QT interval using Fridericia's correction
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	Red blood cell
RDO	Retrieved dropout
RUD Lite	Resource Utilization in Dementia, Lite version
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SMC	Safety Management Committee
SNRI	Serotonin and norepinephrine (noradrenaline) re-uptake inhibitors
SOP	Standard operating procedure
3-SPA	3-Sulfopropanioc acid
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Definition
TBD	To be determined
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TRT	Treatment group
TSH	Thyroid-stimulating hormone
t-tau, T-tau	Total tau
ULN	Upper limit of normal
UP	Unanticipated problem
V	Visit
vMRI	volumetric magnetic resonance imaging
w	Week

1. PROTOCOL SYNOPSIS

Abbreviated Title	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy, Safety and Biomarker Effects of ALZ-801 in Subjects with Early Alzheimer's Disease and APOE4/4 Genotype
Short Title	Phase 3 Study of ALZ-801 in APOE4/4 Early AD Subjects
Sponsor	Alzheon Inc.
Clinical Indication	Early Alzheimer's Disease (AD)
Study Phase	3
Number of Arms	2
Treatment Groups	ALZ-801 265mg or placebo twice per day (BID)
Active Ingredient	The active ingredient is tramiprosate: (S)-3-(2-amino-3-methylbutanamido) propane-1-sulfonic acid ALZ-801, a prodrug of tramiprosate, is tramiprosate conjugated to the amino acid valine.
Assignment	Randomized, double-blinded
Treatment Duration	18 months
Estimated Date First Subject Enrolls	May 2021
Estimated Date Last Subject Completes Study	August 2024
Primary Objectives	<u>Primary Clinical</u> • To evaluate the efficacy of oral ALZ-801 on cognition in subjects with Early AD who are homozygous for the ε4 variant of the Apolipoprotein E gene (APOE4 homozygous or APOE4/4) using the 13-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog 13) • To evaluate the safety and tolerability of ALZ-801 over 78 weeks in Early AD subjects with the APOE4/4 genotype

	Primary Fluid Biomarkers • To evaluate the effects of ALZ-801 on fluid biomarkers of core AD pathology (phosphorylated tau [p-tau]): o Cerebrospinal fluid (CSF) biomarker: tau phosphorylated at threonine 181 (p-tau$_{181}$) in CSF sub-study o Plasma p-tau$_{181}$ in all subjects Primary Imaging Biomarker • To evaluate the effects of ALZ-801 on hippocampal volume using volumetric magnetic resonance imaging (vMRI)
Secondary Objectives	Key Secondary Clinical • To evaluate the effects of ALZ-801 on functional, disability, and composite cognitive/functional outcomes: o Amsterdam Instrumental Activities of Daily Living (A-IADL) o Clinical Dementia Rating – Sum of Boxes (CDR-SB) o Disability Assessment for Dementia (DAD) Additional Secondary Clinical • To evaluate the effects of ALZ-801 on neuropsychiatric symptoms of AD: o Neuropsychiatric Inventory (NPI, 12-item form) • To evaluate the effects of ALZ-801 on additional measures of cognition: o 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog 11) o Mini-Mental State Examination (MMSE) • To evaluate the effects of ALZ-801 on quality of life (QoL): o Quality of Life in Alzheimer's Disease (QoL-AD) • To assess levels of healthcare and caregiver resource usage: o Resource Utilization in Dementia, Lite version (RUD Lite) Secondary Fluid Biomarkers • To evaluate the effects of ALZ-801 on other CSF biomarkers of core AD pathology, neurodegeneration, and neuroinflammation in the CSF sub-study: o Core AD pathology: tau phosphorylated at threonine 217 (p-tau$_{217}$), beta amyloid (Aβ40, Aβ42) o Neurodegeneration in AD: Neurofilament Light (NfL) and total tau (t-tau) o Synaptic toxicity: neurogranin o Neuroinflammation: sTREM2 (microglia), and astrocytic markers YKL-40 and glial fibrillary acidic protein (GFAP)

	• To evaluate the effects of ALZ-801 on other plasma biomarkers of AD pathology, neurodegeneration and neuroinflammation in all subjects:
	  ○ Core AD pathology: p-tau$_{217}$, Aβ40, Aβ42
	  ○ Neurodegeneration: NfL
	  ○ Neuroinflammation: GFAP
	• To evaluate other potential biomarkers of interest in plasma or CSF (to be specified and included in the final statistical analysis plan [SAP])
	<u>Secondary Imaging Biomarkers</u>
	• To evaluate the effect of ALZ-801 on cortical thickness using vMRI
	• To evaluate the effect of ALZ-801 on whole brain volume using vMRI

Other Objectives	<u>Pharmacokinetics</u> • To analyze plasma and CSF levels of ALZ-801 and its metabolites and to build a population pharmacokinetic (PK) model of ALZ-801 in this AD population • To evaluate the correlation of PK measures to clinical efficacy, biomarker, and safety outcomes
Number of Subjects and Sites	Approximately 300 subjects will be recruited; approximately 120 subjects will participate in a CSF sub-study Approximately 85 sites in North America and Europe
Methodology	This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two-arm study, with a treatment duration of 78 weeks (18 months) [Figure 1; Appendix 2]. <u>Study Population</u> The study will enroll male and female subjects, aged 50 to 80 years (inclusive), with a clinical diagnosis of AD, who carry the APOE4/4 genotype, and who are at the early stage of disease (Early AD), which includes Mild Cognitive Impairment (MCI) and Mild Dementia due to AD (Mild AD). • MMSE 22 to 30 (inclusive), • Clinical Dementia Rating (CDR) – Global score of 0.5 or 1 and CDR Memory Box Score ≥ 0.5, • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) delayed memory index score ≤ 85, and • Evidence of progressive memory loss over the last 12 months per investigator assessment

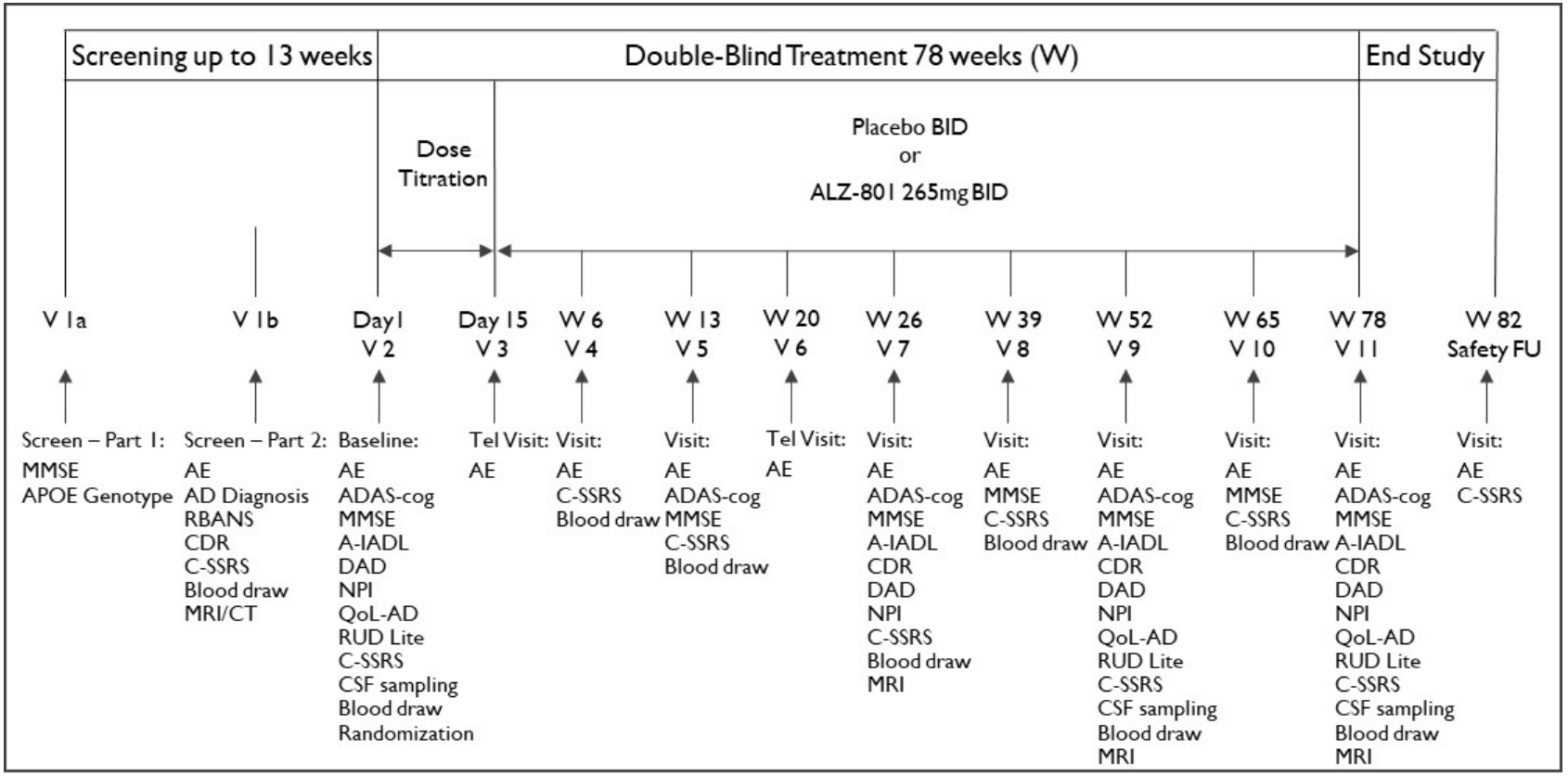
	Study Sample Size Approximately 300 subjects will be enrolled with a goal of having approximately 250 completers. Based on APOE4/4 prevalence of 10% to 15% among AD patients, approximately 3000 AD subjects may need to be pre-screened to identify 300 eligible APOE4/4 subjects. In order to minimize the number of non-APOE4/4 subjects who would otherwise undergo extensive screening tests, screening will be conducted in two parts. Screening – Part 1 (Visit 1a) will include APOE4 genotyping and MMSE testing. Eligible APOE4/4 subjects will enter Screening – Part 2 (Visit 1b) which includes the full screening procedures. It is estimated that out of 3000 AD subjects who undergo Screening – Part 1, approximately 400 subjects will be eligible for Screening – Part 2. Eligible subjects will be randomized 1:1 to receive treatment with oral ALZ-801 or matching placebo (N = 150 each). Approximately 120 subjects (60 per group) will be recruited to participate in a CSF biomarker sub-study. All subjects (150 per group) will provide plasma samples for biomarker and PK assessments. All subjects will participate in the vMRI component of the study. Study Drug All subjects will receive study drug, one tablet BID, taken with a morning and evening meal (or within 30 minutes after each meal) with approximately 10 to 12 hours between doses. Subjects in the placebo treatment arm will receive placebo tablets BID throughout the study. Subjects in the active treatment arm will receive placebo in the morning and a 265mg tablet of ALZ-801 in the evening during the first two weeks of the study; thereafter, they will receive a 265mg tablet BID. This dose provides plasma exposures equivalent to tramiprosate (the active moiety) 150mg BID, which showed promising efficacy in APOE4/4 subjects in a Phase 3 program. This level of tramiprosate exposure showed full inhibition of amyloid oligomer formation in an *in vitro* assay. ALZ-801 will be provided as immediate release tablets (cGMP grade) for oral administration. On clinic visit days, only one dose of study drug will be taken from one of the newly dispensed blister cards and administered at the study site. Duration of Treatment Treatment duration with study drug will be 78 weeks. Subjects will participate in the study for up to 95 weeks: up to approximately 13 weeks for Screening, 78 weeks of treatment, and 4 weeks until the Safety Follow-up Visit.

	Subjects who discontinue the study drug during the trial will be encouraged to remain in the study (off study drug) for continued follow-up by attending Week 52 and Week 78 visits with select study-related procedures performed [retrieved dropouts (RDO)]. For those subjects who choose to completely withdraw from the study at any point, they will be encouraged to return at Week 78 to finish the aforementioned procedures.
Key Inclusion & Exclusion Criteria	<u>Key Inclusion Criteria</u> 1. Male or female between the ages of 50 and 80 years (inclusive) at the Screening – Part 1 Visit. 2. Clinical diagnosis of MCI or Mild Dementia due to AD consistent with the National Institute on Aging-Alzheimer's Association (NIA-AA) Working Group Criteria. 3. Homozygous for the ε4 allele of the apolipoprotein E gene (APOE4/4). 4. MMSE score of 22 to 30 (inclusive) at the Screening – Part 1 Visit. 5. CDR – Global score of 0.5 or 1 and CDR Memory Box Score ≥ 0.5. 6. RBANS delayed memory index score ≤ 85. 7. Evidence of progressive memory loss over the last 12 months per investigator assessment. <u>Key Exclusion Criteria</u> 1. Brain magnetic resonance imaging (MRI) indicative of significant abnormality per central reader, other than AD related atrophy. Computed tomography (CT) scan acceptable for subjects who can not undergo MRI (CT is not allowed for subjects at sites in Germany). 2. Diagnosis of a neurodegenerative disorder other than AD. 3. Diagnosis of major depressive disorder (MDD) within one year prior to the Baseline Visit (Visit 2). 4. Currently taking memantine or has taken memantine within 12 weeks prior to the Baseline Visit. 5. History of suicidal behavior within one year prior to the Baseline Visit or has ongoing suicidal ideation. 6. History of seizures, excluding febrile seizures of childhood or a single distant seizure (≥ 5 years prior to the Baseline Visit). 7. Medically confirmed history of recent cerebral infarct or transient ischemic attack within one year prior to the Baseline Visit.

Estimated Duration of Study	Sponsor estimates the study will be approximately 42 months from the time the first subject signs the informed consent form (ICF) to the last subject participation (last subject, last visit).
Statistical Considerations	<u>Primary Efficacy Endpoint</u> • Cognitive Endpoint: Change from baseline (CBL) to Week 78 in ADAS-Cog 13 scores <u>Primary Fluid Biomarker Endpoints</u> • CBL to Week 78 in CSF p-tau$_{181}$ (in CSF sub-study) • CBL to Week 78 in plasma p-tau$_{181}$ in all subjects <u>Primary Imaging Biomarker Endpoint</u> • CBL to Week 78 in total hippocampal volume as assessed by vMRI <u>Safety and Tolerability</u> • Incidence and nature of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to withdrawal. • CBL in vital signs and physical exam, including body weight • CBL in laboratory parameters (clinical chemistry, hematology, coagulation tests) • CBL in 12-lead electrocardiogram (ECG) parameters. • CBL in MRI central readings for amyloid-related imaging abnormalities with vasogenic edema (ARIA-E) or due to haemosiderin deposition (ARIA-H) • CBL in the Columbia-Suicide Severity Rating Scale (C-SSRS) <u>Analysis Population</u> The primary efficacy population will be the Modified Intent-To-Treat (mITT) Population, which is defined as all randomized subjects who have received at least one dose of study drug, have one baseline assessment, and have also completed at least one scheduled post-baseline visit with at least one valid post baseline assessment. <u>Analysis of Primary Efficacy Endpoints</u> Analyses of the primary efficacy endpoint (CBL in ADAS-Cog 13 scores) will be performed on the mITT Population using on-treatment observed case (OC) data. Effects between treatment groups will be assessed using a mixed effects model with repeated measures (MMRM) that includes treatment and stratification factors: use of concomitant AD medications [acetyl cholinesterase inhibitors or none], age group (50 through 65 years or > 65 years at the Screening

	– Part 1 Visit), gender, disease severity based on MMSE at the Baseline Visit, baseline ADAS-Cog 13 values, visit (VISIT), and treatment by visit interaction. Justification of the Sample Size For the primary efficacy outcome of ADAS-Cog 13, this study is powered to detect a 3.0 point difference between ALZ-801 and placebo in the CBL to Week 78. This assumes a within-treatment SD of approximately 8.1 in the drug arm and 5.6 in the placebo arm. A sample size of 125 subjects per arm will provide approximately 90% power to show a 3-point difference between the two treatment groups at a significance level of $\alpha = 0.05$ (2-sided). The drop-out rate is estimated to be approximately 17% at 78 weeks, thus a total of 300 subjects enrolled would provide approximately 250 completers or approximately 125 per arm.

Figure 1 Study Schema of Study ALZ-801-AD301: Overview of Study Structure and Visits (Detailed Schedule of Assessments in Appendix 2)



AD: Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale – cognitive subscale; AE: adverse event; A-IADL: Amsterdam Instrumental Activities of Daily Living; APOE: apolipoprotein E; BID: twice per day; CDR: Clinical Dementia Rating; CSF: cerebrospinal fluid; C-SSRS: Columbia-Suicide Severity Rating Scale; CT: computed tomography (not allowed for subjects at sites in Germany); DAD: Disability Assessment for Dementia; ECG: electrocardiogram; FU: follow-up; MMSE: Mini-Mental State Exam; MRI: magnetic resonance imaging; NPI: Neuropsychiatric Inventory; PK: pharmacokinetics; QoL-AD: Quality of Life in Alzheimer's Disease; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RUD Lite: Resource Utilization in Dementia, Lite version; Tel: telephone; V: visit; W: week

2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

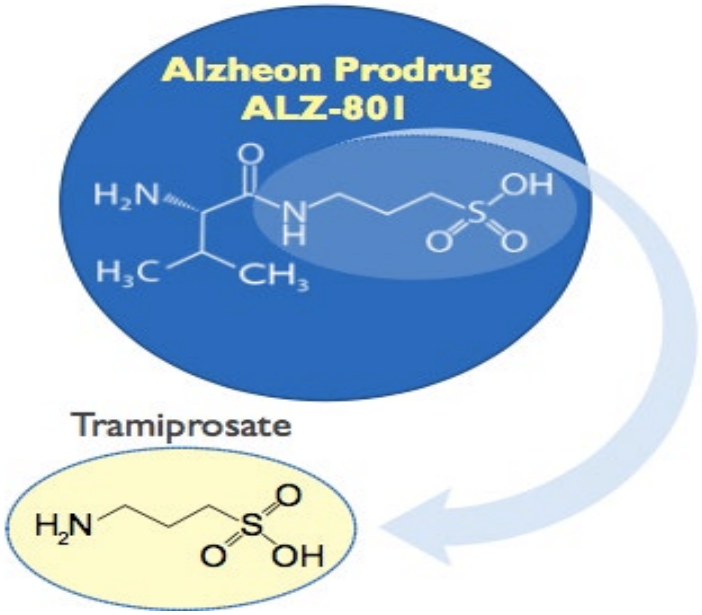
ALZ-801 is an oral agent that is being developed as a potential disease modifying treatment for AD. This 78-week Phase 3 study will focus on Early AD subjects who carry the APOE4/4 genotype, and is designed according to current regulatory guidance for trials in symptomatic patients with Early AD.

The active agent in ALZ-801 is tramiprosate, a small molecule that inhibits the formation of soluble beta amyloid (Aβ42) oligomers [Kocis et al. 2017; Liang et al. 2019]. Tramiprosate had been evaluated in 5 clinical trials in AD patients, across all apolipoprotein E (APOE) genotypes. In a Phase 3 trial in Mild to Moderate AD, efficacy was not achieved in the overall study population, but a meaningful signal was observed in subjects who are either heterozygous or homozygous for the ε4 allele of apolipoprotein E gene (APOE4 carriers), which was further analyzed to identify the optimal study population. Tramiprosate showed promising clinical efficacy in APOE4 homozygotes and heterozygtoes subgroups [Abushakra et al. 2016]. These positive clinical effects were especially significant in APOE4/4 homozygotes [Abushakra et al. 2017] and were observed at a tramiprosate dose (150mg BID) that showed favorable long term safety.

In the Phase 3 studies which included 2025 AD patients, oral tramiprosate showed favorable long-term safety over 2.5 years, with nausea and vomiting being the main TEAEs. There were no events of vasogenic edema in these studies. PK analyses from these studies also showed high variability in plasma levels of tramiprosate. ALZ-801 was therefore developed as a pro-drug of tramiprosate to improve its oral bioavailability and gastrointestinal (GI) tolerability. ALZ-801 is composed of tramiprosate conjugated to the essential amino acid valine [Figure 2]. Upon absorption into systemic circulation, ALZ-801 is rapidly converted into free tramiprosate and valine.

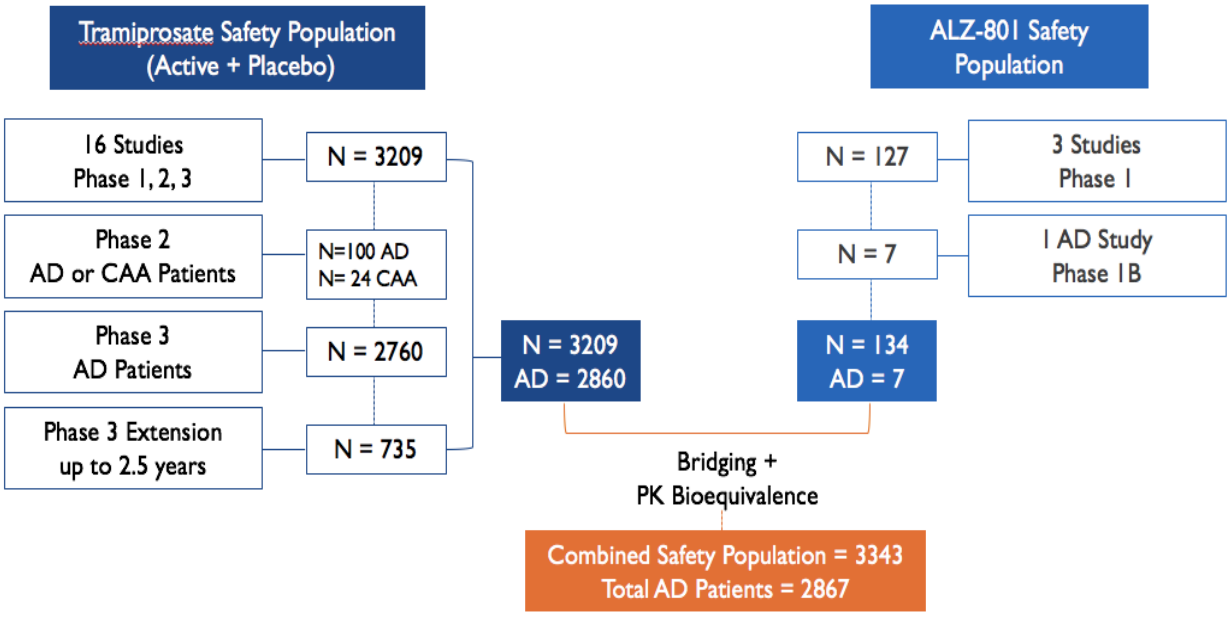
The development of ALZ-801 was based on a bridging strategy to tramiprosate data. The bridging approach was discussed with the US FDA, which requested nonclinical safety and clinical PK and safety studies to compare ALZ-801 and tramiprosate. Nonclinical safety studies showed enhanced safety margins with ALZ-801 [Data on file]. ALZ-801 was evaluated in four bridging studies in 134 subjects, including elderly and AD subjects. These studies allowed the selection of an ALZ-801 dose (265mg BID) that provides plasma levels bioequivalent to tramiprosate 150mg BID that showed efficacy in APOE4/4 homozygotes. In these Phase 1b studies, ALZ-801 showed improved GI tolerability with reports of mild and transient nausea.

Figure 2 **ALZ-801: A pro-drug of tramiprosate. After absorption into the systemic circulation, ALZ-801 is rapidly and fully converted into tramiprosate and valine.**



Based on the bridging of ALZ-801 to tramiprosate clinical data, the dose of ALZ-801 (265mg BID) used in this Phase 3 study is linked to and supported by the large safety data of tramiprosate, which includes a substantial number of long-term exposures in AD patients [Figure 3].

Figure 3 **Large Combined Safety Database of Tramiprosate & ALZ-801**



AD: Alzheimer's disease; CAA: cerebral amyloid angiopathy

In addition to the systematic analysis of clinical efficacy data from the tramiprosate Phase 3 study, volumetric MRI data was previously published [Gauthier et al. 2009]. The vMRI analyses of the North American Phase 3 study showed a dose-dependent, and significant, decrease in hippocampal atrophy, supporting the clinical data. Fluid biomarkers of AD pathology have advanced greatly and will be evaluated in this study to understand the effect of ALZ-801 on disease pathogenesis.

A disease-modifying treatment for AD that provides meaningful efficacy with a favorable safety profile remains a major unmet need. In this Phase 3 trial, ALZ-801 is being evaluated in the APOE4/4 population with Early AD, as the initial AD indication. A future study in APOE4 heterozygotes is also being planned.

The efficacy objectives of this Phase 3 study are to prospectively evaluate clinical outcomes, volumetric imaging endpoints, and fluid biomarker effects of oral ALZ-801. The safety objective is to evaluate the long term safety and tolerability of ALZ-801 over 78 weeks.

2.1. Background Information

2.1.1. Disease Background

Clinical and Pathological Features of AD

AD is an irreversible, progressive neurodegenerative disorder, characterized by gradual cognitive and functional decline and personality changes. The early symptoms of AD usually begin with mild memory difficulties and gradually progress to severe cognitive and functional impairment at later stages. AD symptoms typically include changes in memory, verbal fluency, executive function, and judgment, as well as neuropsychiatric or behavioral symptoms. As these symptoms progress, they lead to functional loss of complex activities, and later to loss of the basic activities of daily living, requiring dependence on caregivers.

The core neuropathological features of AD are the presence of amyloid plaques and neurofibrillary tangles (NFT), and neuronal loss [DeTure & Dickson, 2019]. Amyloid plaques consist of misfolded aggregates of Aβ40 and Aβ42 peptides, and NFT consist of misfolded hyperphosphorylated tau protein. Brain MRI studies in AD patients show progressive cortical atrophy and ventriculomegaly, reflecting progressive neurodegeneration.

Biological Definition of AD

The diagnosis of AD for enrollment in clinical trials has evolved from that of a clinical syndrome to a biological diagnosis based on evidence of the core underlying pathologies. Longitudinal biomarker studies using sensitive CSF biomarkers and positron emission tomography (PET) imaging of amyloid and tau pathologies have elucidated the sequence of events from the presymptomatic stage, to MCI, and to symptomatic AD, leading to a new biomarker based definition of AD [Jack et al. 2018]. These biomarker studies reveal that amyloid pathology starts at least a decade prior to symptom onset, followed by tau pathology, neuronal network dysfunction, microglial activation, neuronal loss, and brain atrophy. With advancing age in individuals at risk of AD, soluble Aβ levels in CSF show the earliest changes with progressive decline in the Aβ42/Aβ40 ratio as amyloid monomers aggregate into soluble oligomers, and insoluble fibrillary forms in the cortex. The insoluble aggregated fibrils and plaques can be detected by amyloid PET imaging. Once amyloid plaque burden reaches a certain threshold, there is a progressive increase of hyperphosphorylated tau reflected as elevation of CSF soluble p-tau, followed by intra-neuronal

tau aggregation and positive tau PET imaging. The tau PET signal is first detected in the medial temporal lobe, and then progressively spreads to other cortical areas. This sequence, of amyloid pathology being upstream of, and driving, tau pathology followed by cognitive decline, was demonstrated in a longitudinal imaging study [Hanseeuw et al. 2019].

CSF biomarkers in AD reflect this cascade of events with early and progressive decrease in Aβ42/Aβ40, followed by progressive elevation of CSF p-tau levels [Blennow et al. 2019]. Though early studies focused on p-tau181 in AD, recent studies suggest that p-tau217 may also be of value as a core AD biomarker [Janelidze et al. 2020a]. The other CSF biomarkers reflect synaptic dysfunction, microglial activation and progressive neuronal injury. Biomarkers of microglial activation and neuroinflammation, such as sTREM2 and YKL-40 respectively, become elevated in AD [Craig-Schapiro et al. 2010; Gispert et al. 2017; Nordengen et al. 2019]. YKL-40 levels are also reported to be higher in APOE4 carriers [Gispert et al. 2017; Wang et al. 2020]. Recent studies have shown elevation of the astrocytic marker GFAP in CSF [Abu-Rumeileh et al. 2020]. Other CSF biomarkers that show progressive elevation are those that reflect synaptic toxicity such as neurogranin [Kvartsberg et al. 2019], and neuronal injury including NfL and t-tau [Mattsson et al. 2016]. Both CSF p-tau$_{181}$ and NfL have shown potential as biomarkers of drug effects in large clinical studies [Budd-Haeberlein et al. 2019; Swanson et al. 2018].

Plasma biomarkers including Aβ42, Aβ40, p-tau$_{181}$, NfL, and t-tau are also being actively studied in AD [Molinuevo et al. 2018]. In particular, recent assays of plasma p-tau and NfL seem promising [Ashton et al. 2019; Mattsson et al. 2019; Mielke et al. 2018]. While plasma NfL may be elevated in other neurodegenerative diseases, p-tau$_{181}$ seems to be specific to AD and has good diagnostic and prognostic value [Janelidze et al. 2020b; Karikari et al. 2020]. Recent studies in AD patients have also shown elevation of the astrocytic marker GFAP in plasma [Verberk et al. 2020]. Plasma p-tau$_{181}$, NfL and GFAP therefore have potential to become valuable non-invasive biomarkers of drug effects in clinical studies.

These advances in fluid biomarkers and PET imaging in AD have led to new AD diagnostic framework for clinical research [Jack et al. 2018]. This diagnostic framework is based on the presence of amyloid and tau pathology, with or without evidence of neuronal injury (A/T/N framework). This framework may be expanded to also include glial activation (A/T/N/G).

APOE4 carriers with cognitive symptoms have high prevalence of positive amyloid PET scans. In longitudinal studies, > 90% of all APOE4 carriers were positive across all ages, and in those aged 50 through 80 years, ≥ 95% had positive amyloid scans [Ossenkoppele et al. 2015]. In APOE4/4 homozygotes evaluated in a drug trial, 98% had positive amyloid scans [Degenhardt et al. 2016].

Eligible subjects will have a clinical diagnosis of AD, carry the APOE4/4 genotype, be at the early stage of disease (Early AD) (i.e., MCI or Mild Dementia due to Alzheimer's disease), and have MMSE score at Screening of 22 to 30 (inclusive), a CDR – Global score of 0.5 or 1 and CDR Memory Box Score ≥ 0.5, an RBANS delayed memory index score ≤ 85, and evidence of progressive memory loss over the last 12 months per investigator assessment.

Since this Phase 3 study is enrolling APOE4/4 homozygotes between the ages of 50 and 80 years with at least a 1 year history of progressive memory deficits, it is expected that ≥ 95% of these patients will have positive amyloid scans.

Since cognitive deficits correlate best with synaptic dysfunction and elevated levels of CSF p-tau, it is expected that enrolled subjects will also have increased CSF p-tau levels at baseline.

Approximately 40% of enrolled subjects will have baseline CSF testing, which will confirm the elevated p-tau$_{181}$ and p-tau$_{217}$ levels.

2.1.2. Current and Emerging Treatments for AD

There is an urgent need for treatments that can meaningfully slow or arrest the progressive cognitive and functional decline of patients with AD (i.e., disease modification). The two classes of approved symptomatic drugs, AChEI and memantine, have not shown efficacy beyond 6 months of treatment. These two classes of drugs, which constitute the current standard of care, target the secondary neurotransmitter deficiencies seen in AD, but do not address the underlying disease pathology. The most advanced drugs in development target the hallmark amyloid pathology. One approach is to promote amyloid clearance using passive amyloid immunotherapy. There are several antibodies in development that target various forms of amyloid: monomers, soluble oligomers, insoluble fibrils, aggregated plaques, or a combination of these forms. Amyloid antibodies, which primarily target monomers, or a combination of monomers and other insoluble amyloid forms, have failed to show efficacy in clinical studies. To date, four amyloid antibodies have shown promising clinical efficacy or biomarker effects in Early AD. These antibodies share one feature: they target soluble amyloid oligomers at least partially, supporting the importance of soluble Aβ oligomers as therapeutic targets [Tolar et al. 2020a, Tolar et al. 2020b]. Aducanumab and lecanemab (BAN2401) have shown promising clinical efficacy and supportive CSF biomarker effects on p-tau$_{181}$ [Budd-Haeberlein et al. 2019; Swanson et al. 2018; Swanson et al. 2020]. A third antibody, donanemab, showed significant but modest effects on composite clinical outcomes, supported by significant effects on plasma p-tau$_{217}$ [Mintun et al. 2021, Sims et al. 2021]. A fourth antibody, gantenerumab, showed significant but small effects on CSF p-tau [Ostrowitzki et al. 2017], and is being evaluated at a higher dose in new Phase 3 trials. In June 2021, aducanumab received "Accelerated Approval" by the US FDA, on the basis of amyloid plaque reduction in Early AD patients [FDA News Release, 2021]. In two identical Phase 3 trials of aducanumab, only one trial showed significant efficacy on the primary clinical outcome.

2.1.2.1. Challenges of Amyloid Immunotherapy

One of the risks of amyloid immunotherapy is the occurrence of vasogenic edema, and microhemorrahges, also called ARIA-E and ARIA-H [Sperling et al. 2011; Salloway et al. 2014]. The risk of ARIA-E is especially elevated in APOE4 carriers, likely related to their higher burden of vascular amyloid. The incidence of ARIA-H (microhemorrhages or haemosiderin deposits) is also increased in subjects who developed ARIA-E. This presents a major development challenge, since the highest doses that showed clinical benefit were associated with high rates of ARIA-E, while lower doses did not provide meaningful efficacy. In clinical trials, ARIA-E was reported in approximately 40% of APOE4 carriers with aducanumab, in 35% of APOE4 carriers with donanemab, and in approximately 15% of APOE4 carriers with BAN-2401 [Budd-Haeberlein et al. 2019, Mintun et al. 2021, Sevigny et al. 2016; Swanson et al. 2018]. Although ARIA-E maybe asymptomatic or mildly symptomatic, some patients developed serious events such as seizures and descreased levels of consciousness. The risk of ARIA requires MRI monitoring in clinical studies, which is burdensome and could limit the utility of these drugs in clinical practice. The delivery of these antibodies as monthly or twice monthly intravenous infusions may be associated with infusion reactions, and is inconvenient to patients and their caregivers.

A convenient oral drug like ALZ-801 that can selectively inhibit the formation of amyloid oligomers at a target efficacious dose that shows favorable safety and tolerability profile would provide a preferable option to immunotherapies. A particular advantage is the low risk of ARIA-E and ARIA-H. This would provide an optimal drug for AD patients who are APOE4 carriers and who constitute 65% to 70% of all AD patients in clinical studies.

2.2. Tramiprosate and ALZ-801

2.2.1. Tramiprosate Background

Tramiprosate, the active agent of oral ALZ-801, is a small molecule that was originally developed as an amyloid anti-aggregation agent, and had shown positive effects in preclinical, *in vitro* and *in vivo*, models of AD [Gervais et al. 2007; Martineau et al. 2010]. In a Phase 2 study in AD patients, tramiprosate showed a dose dependent reduction of Aβ42 levels in CSF, with 50% to 70% reduction at the highest dose of 150mg BID [Aisen et al. 2006]. This dose, 150mg BID, as well as 100mg BID, were evaluated in two Phase 3 studies in Mild to Moderate AD. In the completed North American Phase 3 study, the 150mg BID dose showed cognitive benefits in APOE4 carriers. In APOE4/4 homozygotes, tramiprosate showed dose-dependent efficacy, with significant and meaningful benefits at 150mg BID.

In recent studies further evaluating its mechanism of action, tramiprosate inhibited the formation of soluble Aβ42 oligomers in a dose-dependent fashion, with the highest concentrations fully blocking oligomer formation *in vitro* [Kocis et al. 2017]. This concentration corresponded to the central nervous system concentrations observed with 150mg BID in AD patients [Hey et al. 2018b]. The anti-oligomer effects of tramiprosate were recently replicated by an independent academic group [Liang et al. 2019].

Soluble Aβ oligomers are now thought to play an important role in AD pathogenesis [Selkoe & Hardy 2016; Tolar et al. 2020a; Viola & Klein 2015]. Aβ oligomers appear early in the disease and induce synaptic neurotoxicity and impaired memory [Shankar et al. 2008]. Some forms of Aβ oligomers also trigger tau hyperphosphorylation and other signaling cascades leading to neuronal loss [Jin et al. 2011]. AD patients who are APOE4/4 homozygotes have brain levels of Aβ oligomers that are approximately three times higher than APOE4 non-carriers [Hashimoto et al. 2012], and therefore could potentially benefit from a drug that targets Aβ oligomer formation.

2.2.2. Tramiprosate Mechanism of Action

The mechanism of action of tramiprosate was studied both *in vivo* and *in vitro* [Gervais et al. 2007; Martineau et al. 2010]. Tramiprosate was originally found to maintain Aβ in a non-fibrillary, soluble form resulting in inhibition of neuronal toxicity. *In vivo*, chronic oral tramiprosate treatment of TgCRND8 mice resulted in a significant reduction (~ 30%) in brain amyloid plaque load (quantified via histopathology), and significantly reduced levels of soluble and insoluble Aβ40 and Aβ42 amyloid species. In recent studies, tramiprosate and its active metabolite 3-sulfopropanioc acid (3-SPA) were shown to interact with soluble Aβ monomers to prevent amyloid aggregation by blocking monomeric assembly, thus preventing the formation of soluble toxic oligomer intermediates, from dimers to decamers [Kocis et al. 2017].

New *in vitro* mechanistic studies have been conducted to elucidate the anti-amyloid action of tramiprosate, and its primary metabolite 3-SPA, which has been recently discovered to be an

endogenous molecule in human brain. These studies included computational modeling (i.e., molecular dynamics), NMR and ion-mobility spectrometry-mass spectrometry studies [Hey et al. 2018a; Kocis et al. 2017]. These studies showed that both tramiprosate and 3-SPA inhibit the formation of Aβ42 oligomers by interacting directly with Aβ42 monomers via a molecular "Aβ enveloping action." In addition, these effects occur at tramiprosate concentrations that were achieved at the Phase 3 clinical dose in AD patients [Hey et al. 2018b].

In summary, these studies show that increasing concentrations of tramiprosate and its metabolite, 3-SPA, interact directly with Aβ42 monomers via a molecular "Aβ enveloping action," which in turn, inhibits the formation of toxic Aβ42 oligomers [Hey et al. 2018a; Kocis et al. 2017; Liang et al. 2019]. It is hypothesized that steady state tramiprosate treatment exerts anti-Aβ oligomer effects that are neuroprotective and, over time, will reduce amyloid neurotoxicity, synaptic dysfunction, and neuronal loss, and ameliorate the progressive course of AD.

2.2.3. ALZ-801

ALZ-801 is a pro-drug of tramiprosate, formed by the conjugation of the amino acid valine to tramiprosate (the active agent in ALZ-801). In the original Phase 3 studies with tramiprosate, nausea and vomiting were the most common dose-dependent adverse events (AEs). At the high dose of 150mg BID, drug-related nausea was reported in 14% to 18% of subjects and led to withdrawal in approximately 5% of subjects in the North American study. The plasma levels of tramiprosate showed high intersubject variability. The pro-drug, ALZ-801, was developed to provide enhanced oral absorption, a more consistent PK profile, and improved GI tolerability. The data from several Phase 1b studies with ALZ-801 support this enhanced profile, as described in [Section 2.3.1], and was recently published [Hey et al. 2018b]. Since the pharmacologically active agent in ALZ-801 is tramiprosate, the safety and efficacy of ALZ-801 can be bridged to tramiprosate data when using a bioequivalent dose.

2.2.4. Nonclinical Experience

Nonclinical studies have been conducted with both tramiprosate and ALZ-801 to elucidate the mechanism of action of the compound. Additionally, nonclinical pharmacology, safety pharmacology, PK, metabolism, toxicology, and mutagenicity studies have been conducted in several *in vitro* and *in vivo* models with both tramiprosate and ALZ-801. Results of these studies can be found in the current version of the Investigator's Brochure.

2.3. Rationale for Current Study

The aim for this study is to replicate and confirm the previously described clinical efficacy in APOE4/4 homozygotes with Early AD. The prior tramiprosate data included Mild AD patients with MMSE 22 to 26. Since amyloid oligomer toxicity is thought to be an early event in AD pathogenesis, anti-amyloid agents are likely to show efficacy at earlier stages of AD. Recent AD studies with amyloid antibodies (Aducanumab and BAN2401) have included MCI subjects with MMSE > 26, who have indeed shown promising efficacy. Therefore, ALZ-801 is expected to show positive efficacy when including MCI subjects. The population of Mild AD and MCI subjects is now collectively called Early AD. In addition to cognitive and functional clinical outcomes, ALZ-801 effects on fluid AD biomarkers and downstream effects on hippocampal volume and cortical thickness will also be evaluated.

2.3.1. Clinical Experience

2.3.1.1. Overview of Original Phase 3 Program with Tramiprosate

The tramiprosate Phase 3 program in AD included two Phase 3 placebo-controlled studies of 78 weeks duration: one in North America and the other in Europe. The diagnosis of Mild to Moderate AD in these studies was based only on clinical criteria without biomarker evidence of amyloid pathology. The design of these two studies was almost identical, except that the North American study allowed for use of memantine and anticholinesterase medications as background medication while the European study did not allow use of memantine. These studies included brain MRI imaging in a subset of subjects. the North American study had an open-label safety extension study. The North American study was initiated on 05 August 2004, and the last subject completed the study on 09 February 2007. The co-primary outcomes in the overall population did not achieve statistical significance. When the results of the North American study became available, the European study was still ongoing. The Sponsor of that study, Bellus Health Inc., decided for business reasons to discontinue tramiprosate development and the European study was terminated prior to its completion. The clinical efficacy and safety results of the North American study have been published [Aisen et al. 2011].

The co-primary outcomes in both studies included a cognitive and a composite/functional scale. The cognitive scale was the ADAS-Cog 11 [Rosen et al. 1984], and the composite scale was the CDR-SB [Hughes et al. 1982; Morris 1993], which combines cognitive and functional measures. The secondary outcomes included the functional DAD [Gélinas et al. 1999], the MMSE [Folstein et al. 1975] a cognitive, staging instrument, and the NPI [Cummings 1997], which evaluates the presence and severity of 12 neuropsychiatric symptoms (items) that are common in dementia subjects.

The protocol of the North American study specified analysis by APOE4 genotype, and this analysis was recently undertaken. Phase 3 data were analyzed based on the number of APOE4 alleles (0, 1 or 2). These results were published for the overall, Mild, and Moderate population [Abushakra et al. 2016], and for the Mild subgroup of APOE4/4 patients [Abushakra et al. 2017].

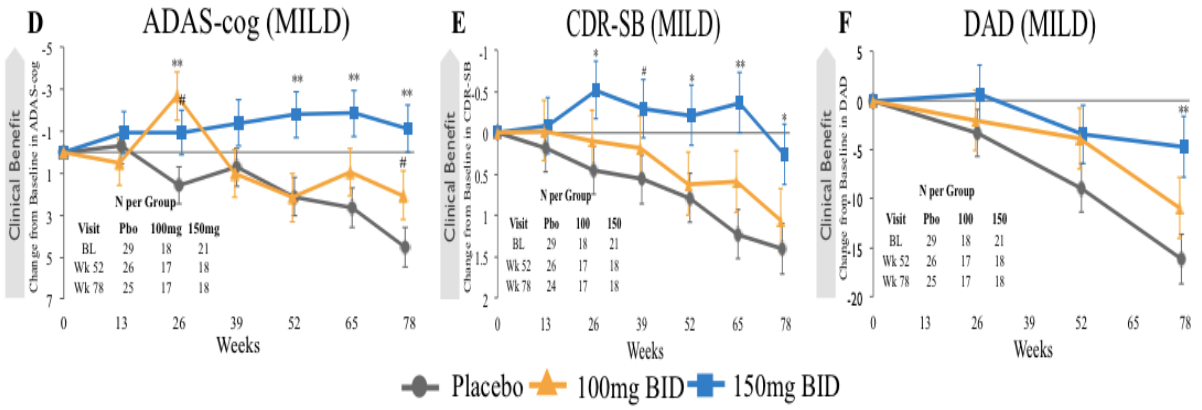
In these efficacy analyses, tramiprosate 150mg BID showed the greatest cognitive efficacy in APOE4/4 homozygotes, intermediate efficacy in heterozygotes, and no efficacy in non-carriers. This difference in efficacy may be explained by the accuracy of AD diagnosis in the study population. These studies predated the current biomarker based diagnosis of AD [Jack et al. 2018]; they did not use amyloid PET imaging or CSF biomarkers as inclusion criteria. Therefore, it is likely that many APOE4 noncarrier patients did not have amyloid pathology underlying their dementia [Ossenkoppele et al. 2015]. Data from solanezumab Phase 3 studies that enrolled a similar population and included an amyloid-PET sub-study, revealed that 98% of APOE4/4 homozygotes and 80% of APOE4 heterozygotes, but only 63% of non-carriers, were amyloid positive [Degenhardt. 2016]. Therefore, tramiprosate showed positive efficacy signals in the subgroups that had the highest diagnostic accuracy and highest rates of amyloid pathology.

Efficacy Data

In APOE4/4 subjects with Mild to Moderate AD, tramiprosate showed significant efficacy on ADAS-Cog, with a numerical benefit on the CDR-SB at 78 weeks. In APOE4/4 subjects with Mild AD, the effects on ADAS-Cog and CDR-SB were larger (ADAS-Cog approximately 5 points; CDR-SB 1.25 points), statistically significant, and sustained at 78 weeks [Figure 4]. These effects

represent cognitive and functional benefits of 125% and 81%, respectively, compared to placebo and are clinically meaningful [Abushakra et al. 2017]. Tramiprosate effects on the DAD also showed significant benefits of 71% compared to placebo [Figure 4].

Figure 4 Tramiprosate Effects in APOE4/4 Subjects with Mild AD (MMSE 22-26) over 78 Weeks



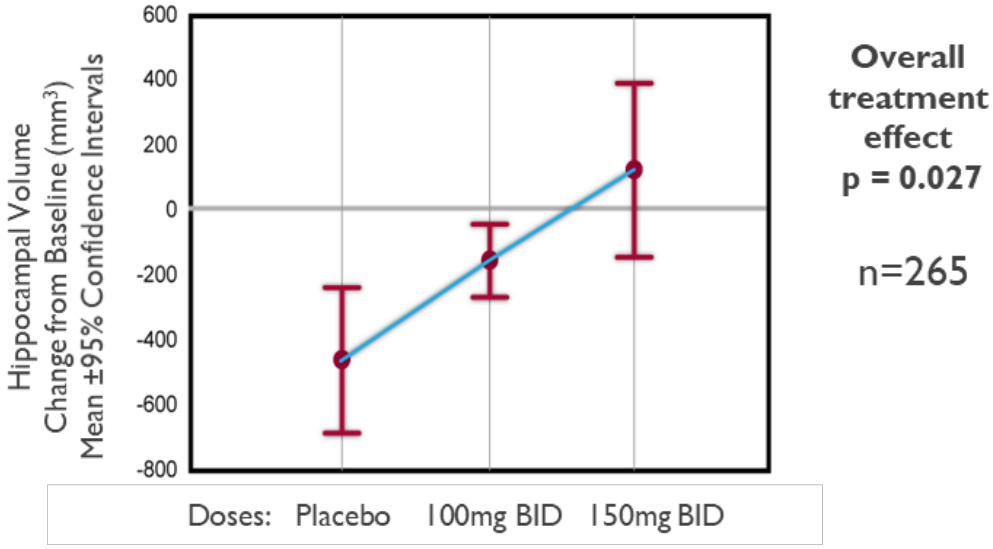
ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; BID: twice per day; CDR-SB: Clinical Dementia Rating – Sum of Boxes; DAD: Disability scale for dementia; MMSE: Mini-Mental State Examination.

Subjects who completed the North American study were enrolled in an extension study where subjects from the 3 dose groups received high dose tramiprosate (150mg BID) for an additional 52 weeks. In the APOE4/4 Mild group, subjects who received high dose tramiprosate over 2.5 years consistently performed better on the ADAS-Cog compared to the placebo-tramiprosate group [Data on file].

Volumetric Imaging Data

In the North American study, there were 265 MRI suitable for volumetric analyses including assessment of hippocampal volumes. These vMRI analyses showed a dose dependent decrease in hippocampal atrophy, as shown in [Figure 5], supporting the clinical data [Gauthier et al. 2009].

Figure 5 Imaging Effects of Tramiprosate: Dose-Dependent Decrease in Hippocampal Atrophy



BID: twice per day

APOE4/4 homozygotes with Mild AD seem to be an ideal population for tramiprosate studies. This finding is consistent with the fact that APOE4/4 homozygotes have high levels of Aβ oligomers [Hashimoto et al. 2012], compared to non-carriers, and that tramiprosate inhibits oligomers at concentrations achieved with the dose used in the North American Phase 3 trial [Kocis et al. 2017].

Based on the above clinical benefits in APOE4/4 subjects, in this study, ALZ-801 at a dose of 265mg BID is expected to provide significant clinical benefit over 78 weeks. This dose has been selected to provide bioequivalent tramiprosate levels (i.e., bridging dose) to the tramiprosate 150mg BID dose used in used in the North American Phase 3 trial.

Safety Data

The combined safety data of both tramiprosate Phase 3 studies includes 2025 subjects treated for up to 78 weeks, and approximately 400 treated up to 130 weeks, and suggests a favorable long term safety profile. In the overall safety population, the most common AEs with incidence > 2 × placebo rates were nausea, vomiting, and weight loss [Abushakra et al. 2016]. The safety profile was similar in the APOE4/4 subjects [Abushakra et al. 2017]. There was a low incidence of serious adverse events (SAEs) leading to withdrawal. Most TEAEs were mild to moderate in severity.

An important safety advantage of tramiprosate was that no cases of ARIA-E (vasogenic edema) were detected by central MRI assessments of 426 AD subjects, including APOE4 carriers [Abushakra et al. 2016].

2.3.1.2. Overview of ALZ-801 Phase 1 and 2 Studies

ALZ-801 was evaluated in a total of 4 Phase 1 studies that included 3 studies in healthy volunteers including elderly subjects, and 1 study in AD patients. The Phase 1 studies in volunteers included:

(1) a single ascending dose (SAD) study; (2) a 14-day multiple ascending dose (MAD) study; and (3) a single-dose tablet food effect study. The detailed PK, safety and tolerability results of these studies were published [Hey et al. 2018b], and described in the Investigator's Brochure.

In summary, ALZ-801, when administered in capsule and tablet forms, showed excellent oral safety and tolerability in healthy adults and elderly volunteers, with decreased incidence of nausea. These studies showed significantly improved PK characteristics over oral tramiprosate, with markedly decreased inter-subject variability in tramiprosate plasma levels. A clinical dose of ALZ-801 (265mg BID) was established that achieves the target area under the concentration-time curve (AUC) exposure of 150mg BID of tramiprosate in plasma, which had shown positive clinical effects in APOE4/4 AD subjects in the North American Phase 3 study.

ALZ-801 safety and PK was also evaluated in AD subjects, in an open-label Phase 1b study of 2 weeks duration. This study enrolled 7 AD subjects who had either the APOE4/4 or APOE3/4 genotype. PK analyses from this study confirmed the favorable steady-state characteristics of ALZ-801 with improved elimination half-life and reduced plasma variability of tramiprosate. All subjects completed the study and no SAEs were reported [Data on file] ALZ-801 also demonstrated improved GI tolerability, with only mild and transient AEs of nausea.

The biomarker effects of ALZ-801 are currently being evaluated in a Phase 2 study (Study AD201) in approximately 40 Early AD subjects with either APOE4/4 or APOE3/4 genotype. Subjects will receive ALZ--01 at 265mg BID over 2 years, and provide serial CSF and plasma for AD biomarkers, vMRI assessments, and exploratory cognitive outcomes.

2.3.2. Rationale for Development in APOE4/4 Subjects

<u>High Burden of Extracellular Aggregated β-Amyloid</u>

The APOE4 allele is the strongest genetic risk factor for the development of sporadic AD. It confers a 4- to12-fold higher risk of developing AD with an earlier age of onset, with APOE4/4 subjects being at highest risk [Farrer et al. 1997; Roses 1996]. APOE4 carriers accumulate more amyloid pathology and at a faster rate than non-carriers [Jansen et al. 2015; Kim et al. 2009; Ossenkoppele et al. 2015]. In amyloid imaging studies, the prevalence of amyloid pathology was highest in APOE4/4 subjects, followed by heterozygotes, and lowest in APOE4 non-carriers [Jansen et al. 2015]. In the clinical study population, positive amyloid scans were found in 98% of homozygotes, 80% of heterozygotes, and only 63% of non-carriers [Degenhardt et al. 2016]. In AD and MCI, CSF Aβ42 showed an APOE4 gene-dose effect, with the lowest (most abnormal) levels in APOE4/4 homozygotes followed by APOE4 heterozygotes [Lautner et al. 2014; Prince et al. 2004]. APOE4 carriers also show faster rates of cognitive decline at the MCI and AD stages [Caselli et al. 2009; Martins et al. 2005; Petersen et al. 2005].

Consistent with the higher amyloid burden, APOE4/4 subjects exhibit an earlier and faster rate of cognitive decline compared to APOE4 non-carriers [Breitner et al. 1999; Cosentino et al. 2008; Rogers et al. 2012], becoming symptomatic approximately a decade earlier.

<u>High Burden of Aggregated β-Amyloid in Vasculature</u>

APOE4 carriers also develop more vascular amyloid pathology [Chalmers et al. 2003; Schmechel et al. 1993], which may underlie their increased risk of ARIA-E with amyloid immunotherapies. From a safety perspective, APOE4 carrier AD patients, especially APOE4/4 homozygotes, have a clear need for an agent that delivers efficacy without the increased risk of ARIA-E.

High Burden of Soluble β-Amyloid Oligomers

The APOE4/4 genotype is associated with higher levels of soluble Aβ oligomers [Hashimoto et al. 2012; Tai et al. 2013], which are known to be highly synaptotoxic [Viola & Klein 2015]. Since ALZ-801 inhibits the formation of Aβ oligomers [Kocis et al. 2017], APOE4/4 homozygotes would be an ideal population to evaluate its efficacy [Tolar et al. 2020a]. Indeed, in the Phase 3 NA study, tramiprosate showed meaningful clinical efficacy in APOE4 carriers, especially APOE4/4 [Abushakra et al. 2016; Abushakra et al. 2017]. Clinical efficacy in APOE4/4 subjects will be confirmed in this ALZ-801 Phase 3 trial (Study AD301).

To date, no other program has specifically targeted symptomatic APOE4/4 subjects with cognitive and early functional deficits. Therefore, APOE4/4 subjects with Early AD who are already receiving symptomatic medications represent a population with urgent treatment needs. This Phase 3 study will be in APOE4/4 homozygotes, and a study in APOE4 heterozygotes is being planned.

2.3.3. Rationale for Choice of Clinical Outcomes

The clinical data in APOE4/4 Mild AD subjects from the North American study [Abushakra et al. 2017], had shown statistically (nominally) significant and clinically meaningful effects on the co-primary outcomes ADAS-Cog 11 and CDR-SB, and on the DAD. The magnitude of benefit was highest with ADAS-Cog 11, followed by the functional outcomes. A similar pattern of efficacy has been shown with BAN-2401 and aducanumab, where ADAS-Cog effects were more robust that the CDR-SB [Budd-Haeberlein et al. 2019; Swanson et al. 2018].

At earlier stages of the disease, cognition is expected to decline before function, making cognitive outcomes a good choice in earlier stage AD studies. This is consistent with the findings in BAN-2401 and aducanumab studies, where ADAS-Cog 13 effects were more robust than CDR-SB effects in Early AD patients [Budd-Haeberlein et al. 2019; Swanson et al. 2018]. Since this Phase 3 study will enroll Early AD subjects, ADAS-Cog 13 will be designated the primary efficacy outcome. The ADAS-Cog 13 includes the original 11 items, plus 2 items assess executive tasks.

The cognitive outcome will be supported by a functional scale, namely the A-IADL, which is designated a key secondary outcome with appropriate step-down analysis.

The other functional outcomes, DAD and CDR-SB will be additional secondary outcomes. The ADAS-Cog 11 will also be included as a secondary outcome, since it has been used in other AD studies. The 12-item NPI will be used to assess behavioral effects of ALZ-801.

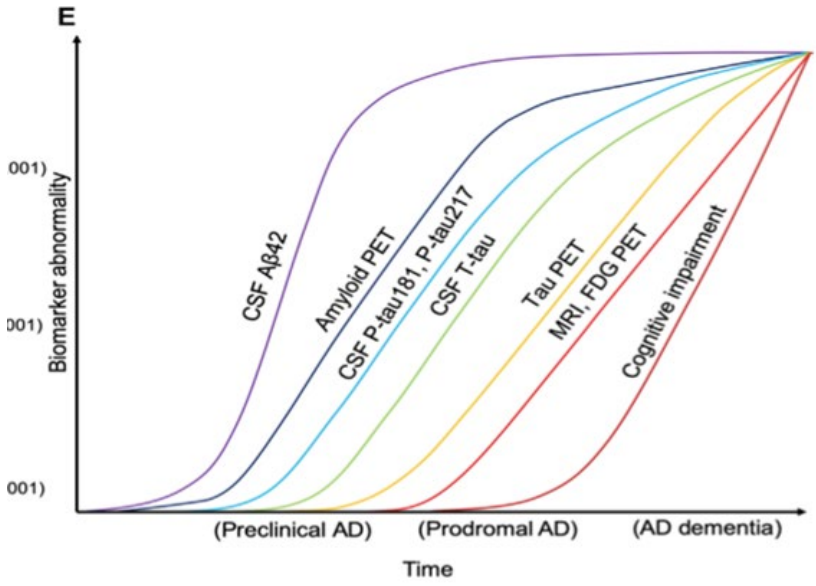
2.3.4. Rationale for Fluid Biomarker and MRI Assessments

Longitudinal studies in AD subjects have shown that amyloid levels, as they increase in brain, induce abnormal phosphorylation of neuronal tau, and a progressive elevation of p-tau in CSF. This progressive increase in CSF p-tau precedes the appearance of intraneuronal NFTs, the tau pathology that can be detected by tau PET-imaging [Mattsson-Carlgren et al. 2020]. Increases in toxic amyloid oligomers and p-tau induce downstream synaptic dysfunction, microglial activation, and neuronal injury [Figure 6].

Since ALZ-801 inhibits the formation of toxic soluble Aβ42 oligomers, it is expected to inhibit the downstream effects of toxic Aβ42 oligomers, namely formation of p-tau$_{181}$ and other p-tau isoforms. Two other late stage anti-amyloid antibodies (BAN2401 and aducanumab) that target Aβ oligomers at least partially, have shown clinical efficacy in Early AD patients, and have shown

significant lowering effects on CSF p-tau$_{181}$ after 78 weeks of treatment [Tolar et al. 2020b]. In Early AD patients, CSF p-tau$_{181}$ levels in the placebo arm remain stable over 78 weeks, while the drug arms induced a dose-dependent and significant (13% to 17%) reduction relative to baseline [Budd-Haeberlein et al. 2019; Swanson et al. 2018].

Figure 6 The Evolution of CSF Biomarker Changes in AD [Mattsson-Carlgren et al. 2020]



Aß: beta amyloid peptide; AD: Alzheimer's disease; CSF: cerebrospinal fluid; FDG PET: fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging: PET: positron emission tomography P-tau: phosphorylated tau; T-tau: total tau.

In another study in Early (Prodromal) AD with the anti-amyloid antibody, gantenerumab, CSF p-tau$_{181}$ in the placebo arm was also stable over 104 weeks, while the highest antibody dose reduced p-tau$_{181}$ by < 8%, and there was no evidence of clinical efficacy at that dose. [Ostrowitzki et al. 2017]. Therefore, a consistent reduction in CSF p-tau$_{181}$ is observed with two antibodies that share the anti-oligomer mechanism of action and show promising cognitive benefits. Since ALZ-801/tramiprosate is an anti-oligomer agent with promising clinical efficacy in APOE4 carriers (similar to BAN2401 and aducanumab), it is expected that ALZ-801 will decrease CSF p-tau$_{181}$ by at least 15% compared to placebo. To date, no studies have reported drug effects on CSF p-tau$_{217}$, but this will be evaluated in this trial.

The two anti-amyloid agents (aducanumab and BAN2401) have also shown effects on downstream CSF biomarkers, namely biomarkers of synaptic injury (neurogranin) and NfL, or on tau-PET imaging [Tolar et al. 2020b]. Therefore the key secondary objectives of this study are to evaluate, in the CSF sub-study, the effects of ALZ-801 on CSF levels of NfL, t-tau (another biomarker of neuronal injury) and neurogranin, and on neuroinflammatory biomarkers known to be involved in AD pathology (sTREM2, YKL-40, GFAP).

For plasma biomarkers of AD, well performing plasma assays for p-tau$_{181}$, NfL and GFAP were recently reported [Karikari et al. 2020; Mattsson et al. 2019; Verberk et al. 2020]. Plasma levels

of p-tau$_{181}$ and NfL are designated as key secondary fluid biomarker outcomes, and plasma GFAP will be evaluated as an additional secondary outcome. CSF and plasma levels of soluble Aβ42/ Aβ40 will also be evaluated.

Hippocampal volume and cortical thickness are commonly included as volumetric imaging biomarkers in AD, and are especially relevant in APOE4 carriers [Hostage et al, 2013]. Both measures show accelerated atrophy in APOE4/4 homozygotes with Early AD compared to APOE3/3 subjects [Abushakra et al. 2020]. Tramiprosate, the active agent in ALZ-801, had shown protective effects on hippocampal volume in the Phase 3 North American study [Gauthier et al. 2009]. Therefore, ALZ-801 is expected to decrease hippocampal atrophy and loss of cortical thickness at 78 weeks. Hippocampal volume is designated as primary imaging outcome, and cortical thickness as an additional outcome.

The study will also allow PK-pharmacodynamic correlations between exposures of tramiprosate (and its metabolite) in plasma/CSF, clinical outcomes, and biomarker effects.

This study will also further support the long term safety and tolerability of ALZ-801 in AD patients with the APOE4/4 genotype.

2.4. Potential Risks and Benefits

Tramiprosate, the active agent of ALZ-801, has been studied in 3295 adults across 16 clinical studies, including 2800 AD subjects. The Phase 3 studies included 2025 subjects treated for up to 78 weeks, of whom 714 subjects were treated for up to 52 additional weeks in an extension study. Therefore, a total of 371 AD subjects received tramiprosate for up to 2.5 years. In the controlled Phase 3 studies, the most common AEs showing dose-dependence were GI in nature and included nausea, vomiting, and weight loss. Nausea and vomiting were mostly mild to moderate, led to low number of withdrawals, and likely represent local effects of tramiprosate on the GI mucosa.

In the safety extension study, the most common AEs were falls, nausea, urinary tract infection, and diarrhea; typically seen in AD studies. There was no organ toxicity with long-term treatment.

The other AEs were representative of the comorbidities seen in this population and, therefore, no specific risks were identified. The AE profile seemed similar among the APOE4 non-carriers and the APOE4 heterozygous and APOE4/4 homozygous subgroups.

Central brain MRI assessments from 426 subjects in the tramiprosate Phase 3 studies, of whom 254 were APO4 carriers, showed no occurrence of vasogenic edema (ARIA-E) on active drug.

The benefits seen in APOE4/4 subjects with Mild AD include lesser decline in cognition and function over 78 weeks, and lower disability scores. These effects were demonstrated in subjects already receiving maximum standard of care; therefore, representing additional benefits of tramiprosate treatment.

Safety data from the ALZ-801 Phase 1 program which included AD patients and healthy volunteers supports improved GI tolerability especially when taken with food. This protocol requires that ALZ-801 be taken with or within 30 minutes after food.

Based on the promising efficacy in APOE4/4 subjects and the favorable safety profile in all subjects including APOE4 carriers, tramiprosate seems to provide a favorable benefit risk profile in subjects with Mild or Early AD. ALZ-801 at a dose of 265mg BID will provide equivalent

exposures to tramiprosate 150mg BID, and is expected to provide a favorable benefit-risk profile in APOE4/4 homozygotes with AD.

3. OBJECTIVES AND PURPOSE

3.1. Objectives

3.1.1. Primary Objectives

Primary Clinical

- To evaluate the efficacy of oral ALZ-801 on cognition in subjects with Early AD who are homozygous for the ε4 variant of the APOE gene (APOE4 homozygous or APOE4/4) using ADAS-Cog 13
- To evaluate the safety and tolerability of ALZ-801 over 78 weeks in Early AD subjects with the APOE4/4 genotype

Primary Fluid Biomarkers

- To evaluate the effects of ALZ-
- 801 on fluid biomarkers of core AD pathology (p-tau):
  - CSF biomarker: p-tau$_{181}$ (in CSF sub-study)
  - Plasma p-tau$_{181}$ in all subjects

Primary Imaging Biomarker

- To evaluate the effects of ALZ-801 on hippocampal volume using vMRI

3.1.2. Secondary Objectives

Key Secondary Clinical

- To evaluate the effects of ALZ-801 on cognitive and/or functional outcomes:
  - A-IADL
  - CDR-SB
  - DAD

Additional Secondary Clinical

- To evaluate the effects of ALZ-801 on neuropsychiatric symptoms of AD:
  - NPI (12-item form)
- To evaluate the effects of ALZ-801 on additional measures of cognition:
  - ADAS-Cog 11
  - MMSE

- To evaluate the effects of ALZ-801 on QoL:
  - QoL-AD
- To assess levels of healthcare and caregiver resource usage:
  - RUD Lite

Secondary Fluid Biomarkers

- To evaluate the effects of ALZ-801 on other CSF biomarkers of core AD pathology, neurodegeneration, and neuroinflammation in the CSF sub-study:
  - Core AD pathology: p-tau$_{217}$, beta amyloid (Aβ40, Aβ42)
  - Neurodegeneration in AD: NfL and t-tau
  - Synaptic toxicity: neurogranin
  - Neuroinflammation: sTREM2 (microglia), and astrocytic markers YKL-40 and GFAP
- To evaluate the effects of ALZ-801 on other plasma biomarkers of AD pathology, neurodegeneration and neuroinflammation in all subjects:
  - Core AD pathology: p-tau$_{217}$, Aβ40, Aβ42
  - Neurodegeneration: NfL
  - Neuroinflammation: GFAP
- To evaluate other potential biomarkers of interest in plasma or CSF (to be specified and included in the final SAP)

Secondary Imaging Biomarkers

- To evaluate the effect of ALZ-801 on cortical thickness using vMRI
- To evaluate the effect of ALZ-801 on whole brain volume using vMRI

Pharmacokinetics

- To analyze plasma and CSF levels of ALZ-801 and its metabolites and to build a population PK model of ALZ-801 in this AD population
- To evaluate the correlation of PK measures to efficacy, biomarker and safety outcomes

4. STUDY DESIGN AND ENDPOINTS

4.1. Description of the Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two-arm study, with a treatment duration of 78 weeks (18 months).

Study Population

The study will enroll male and female subjects, aged 50 to 80 years (inclusive), with a clinical diagnosis of AD, who carry the APOE4/4 genotype, and who are at the early stage of disease (Early AD), which includes MCI and Mild AD.

- MMSE 22 to 30 (inclusive),
- CDR – Global score of 0.5 or 1 and CDR Memory Box Score ≥ 0.5,
- RBANS delayed memory index score ≤ 85, and
- Evidence of progressive memory loss over the last 12 months per investigator assessment as captured on the diagnostic verification form

Study Drug

All subjects will receive study drug, one tablet BID, taken with a morning and evening meal (or within 30 minutes after each meal) with approximately 10 to 12 hours between doses. Subjects in the placebo treatment arm will receive placebo tablets BID throughout the study. Subjects in the active treatment arm will receive placebo in the morning and a 265mg tablet of ALZ-801 in the evening during the first two weeks of the study; thereafter, they will receive a 265mg tablet BID. This dose provides plasma exposures equivalent to tramiprosate (the active moiety) 150mg BID, which showed promising efficacy in APOE4/4 subjects in a Phase 3 program. This level of tramiprosate exposure showed full inhibition of amyloid oligomer formation in an *in vitro* assay. ALZ-801 will be provided as immediate release tablets (cGMP grade) for oral administration.

On clinic visit days, only one dose of study drug will be taken from one of the newly dispensed blister cards and administered at the study site.

Study Sample Size

Approximately 300 subjects will be enrolled across approximately 85 study sites in the U.S., Canada, and Europe with a goal of having approximately 250 completers. Based on APOE4/4 prevalence of 10% to 15% among AD patients, approximately 3000 AD subjects may need to be pre-screened to identify 300 eligible APOE4/4 subjects. In order to minimize the number of non-APOE4/4 subjects who would otherwise undergo extensive screening tests, screening will be conducted in two parts. Screening – Part 1 will include APOE4 genotyping, MMSE testing, prohibited medications screening, demographics, and medical history. Eligible subjects will enter Screening Part 2 which includes rest of the screening procedures. It is estimated that, of the approximately 3000 AD subjects who undergo Screening – Part 1, approximately 400 subjects will be eligible for Screening – Part 2.

Eligible subjects will be randomized 1:1 to receive treatment with oral ALZ-801 or matching placebo (N = 150 each). Approximately 120 subjects (60 per group) will be recruited to participate in a CSF biomarker sub-study. All subjects (150 per group) will provide plasma samples for biomarker and PK assessments. All subjects will participate in the vMRI component of the study.

Duration of Treatment

Treatment duration with study drug will be 78 weeks. Subjects will participate in the study for up to 93 weeks: up to 11 weeks for Screening, 78 weeks of treatment, and 4 weeks until the Safety Follow-up Visit.

Study Conduct Duration

It is estimated that it will take approximately 18 months to recruit subjects into the study. The total duration of the study including recruitment, screening, main treatment and safety follow-up will be approximately 42 months.

4.2. Study Endpoints

4.2.1. Primary Endpoints

Primary Efficacy Endpoint

- Cognitive Endpoint: Difference between study drug and placebo in the mean CBL to Week 78 in ADAS-Cog 13 scores

Primary Fluid Biomarker Endpoints

- CBL to Week 78 in CSF p-tau$_{181}$ (in CSF sub-study)
- CBL to Week 78 in plasma p-tau$_{181}$ in all subjects

Primary Imaging Biomarker Endpoint

- CBL to Week 78 in total hippocampal volume as assessed by vMRI

Safety and Tolerability

- Incidence and nature of TEAEs, serious TEAEs, and TEAEs leading to withdrawal
- CBL in vital signs and physical exam, including body weight
- CBL in laboratory parameters (clinical chemistry, hematology, coagulation tests)
- CBL in 12-lead ECG parameters
- CBL in MRI central readings for ARIA-E or ARIA-H
- CBL in the C-SSRS

4.2.2. Secondary Endpoints

Key Secondary Efficacy Endpoint

- CBL to Week 78 in the following scales:
  - A-IADL
  - CDR-SB
  - DAD

Additional Secondary Efficacy Endpoints

- CBL to Week 78 in the following scales:
  - NPI
  - ADAS-Cog 11
  - MMSE
  - QoL-AD
  - RUD Lite
- CBL for the following scales and time points:

- ADAS-Cog 13 and ADAS-Cog 11 scores to Weeks 13, 26, and 52
- A-IADL, CDR-SB, DAD, and NPI scores to Weeks 26 and 52
- MMSE scores to Weeks 13, 26, 39, 52, and 65
- QoL-AD and RUD Lite scores to Week 52

Secondary Fluid Biomarker Endpoints

- CBL to Week 78 in CSF p-tau$_{217}$, Aβ40, Aβ42, NfL, t-tau, neurogranin, sTREM2, YKL-40, and GFAP (in CSF sub-study)
- CBL to Week 78 in plasma p-tau$_{217}$, Aβ40, Aβ42, NfL, and GFAP in all subjects
- CBL to 52 weeks in all CSF biomarkers
- CBL to Weeks 13, 26, 39, 52, and 65 in all plasma biomarkers
- CBL to Weeks 13, 26, 39, 52, 65, and/or 78 for other potential biomarkers of interest in plasma or CSF, including assay of CSF Aβ oligomers (to be specified and included in the final SAP)

Secondary Imaging Biomarker Endpoints

- CBL for the following MRI measures:
  - Total hippocampal volume to Weeks 26 and 52
  - Cortical thickness and whole brain volume to Weeks 26, 52, and 78

4.2.3. Other Endpoints

Pharmacokinetic Endpoints

- Plasma and CSF levels of ALZ-801, tramiprosate, and metabolite 3-SPA at each visit in the study, and update of the population PK model
- Correlation of PK levels to efficacy and biomarker outcomes
- Correlation of PK levels to safety parameters

5. STUDY ENROLLMENT AND WITHDRAWAL

The study population will include subjects, aged 50 to 80 years (inclusive), who have a clinical diagnosis of Early AD and who carry the APOE4/4 genotype.

All Screening assessments must be completed and reviewed to confirm the potential subject meets all eligibility criteria.

5.1. Inclusion Criteria

To be considered eligible to participate in the study, the subject must meet all of the following requirements:

1. Be male or female between the ages of 50 and 80 years (inclusive) at the Screening – Part 1 Visit.

2. Has a clinical diagnosis of MCI or Mild Dementia due to AD consistent with the NIA-AA Working Group Criteria [Albert et al. 2011; Jack et al. 2018; McKhann et al. 2011].
3. Is homozygous for the ε4 allele of the APOE gene (APOE4/4).
4. Has an MMSE score of 22 to 30 (inclusive) at the Screening – Part 1 Visit.
5. Has a CDR Global score at Screening of 0.5 or 1, and a CDR Memory Box score ≥ 0.5.
6. Has an RBANS delayed memory index score ≤ 85.
7. Has evidence of progressive memory loss over the last 12 months per investigator assessment as captured on the diagnostic verification form.
8. Can complete the cognitive testing and all other required study procedures.
9. Has completed at least 6 years of formal education after age of 5 years, and is able to read at minimum of 6th grade level or equivalent per investigator assessment.
10. Lives at home independently, in a senior living facility, or in an assisted living facility.
11. Has a body mass index (BMI) between 17-40 (inclusive).
12. Except for a diagnosis of AD and the presence of stable medical conditions, is, in the opinion of the Investigator, in good general medical health based upon the results of medical history, physical examination, laboratory tests, vital signs, and ECG.
13. Has a reliable caregiver or study partner who is willing and able to sign an ICF, to accompany the subject to study visits, and adhere to study requirements (The caregiver or study partner, in the Investigator's opinion, has adequate contact with the subject to be able to provide accurate information about the participant's cognitive and functional abilities).
14. Is willing to sign an IRB/IEC approved informed consent document indicating that he/she understands the purpose of the study and the procedures that are required for the study, and that he/she is willing to participate in the study. If a subject is unable or deemed not competent to sign the consent form, the subject's legally authorized representative may sign the consent form with the subject's assent, except where local regulations and IRB/IEC approval do not allow subjects who are unable or deemed not competent to sign the consent form, to participate in the study.

    Note: The subject who participates in the CSF sub-study will sign an additional ICF specific for the sub-study.
15. Both subject and caregiver/study partner are fluent in, and able to read, the local language in which study assessments are administered at the study site.
16. Subject and caregiver/study partner agree to be compliant with study procedures and adhere to study protocol.
17. Subject and caregiver/study partner agree not to receive or administer any prohibited concomitant medications during the study.
18. If female, must be non-breastfeeding, and

    EITHER be of non-childbearing potential, described as either:

- Postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status (FSH analysis will be done at the Screening – Part 2 Visit and FSH levels should be in the postmenopausal range as determined by the laboratory), or
- Documented sterilization procedure (hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy, hysterectomy, or bilateral oophorectomy) at least 6 months prior to the first dose.

OR

- If of childbearing potential, defined as a premenopausal female capable of becoming pregnant, must also have negative serum and urine pregnancy results prior to dosing, and either sexually inactive (sexually abstinent for 14 days prior to the first dose continuing through 28 days after the last dose) or use a highly effective method of contraception (with a failure rate of less than 1% per year when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose.

Note: Highly effective methods include the following:

- intrauterine device (IUD),
- surgical sterilization of the partner (vasectomy for 6 months minimum),
- combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal),
- progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable),
- intrauterine hormone-releasing system (IUS), or
- bilateral tubal occlusion.

19. If male,

    EITHER be non-vasectomized and agrees to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days after the last dose of study medication and the female partner agrees to inclusion criterion 18,

    OR

    be vasectomized at least 6 months prior to first dose and agrees to use a condom during sexual intercourse, or less than 6 months prior to first dose and must follow the same restrictions as a non-vasectomized male.

20. If treated with an AChEI, must be on a stable treatment for at least 12 weeks prior to the Baseline Visit and must be able to continue on the same drug for the duration of the study.
21. If treated with permitted antidepressants, mood stabilizers, or other psychotropic medications, must be on a stable dose according to [Table 1]. Only two anticonvulsants are permitted (for any use) as indicated in Table 1.
22. If taking permitted, non-psychotropic medications for the treatment of non-excluded medical conditions, must be on a stable dose according to [Table 1].

5.2. Exclusion Criteria

To be considered eligible to participate in the study, the subject must not meet any of the following exclusion criteria:

1. Has a screening brain MRI indicative of significant abnormality per central reader, other than AD related atrophy, including, but not limited to,

   - prior large vascular territorial infarct,
   - > 2 lacunar infarcts (size > 1.5 cm) outside the brain stem,
   - severe white matter changes (deep white matter changes Fazekas grade = 3),
   - ventriculomegaly related to normal pressure hydrocephalus (after clinical correlation), or
   - aneurysm, subdural hematoma, abscess, or brain tumor (other than meningiomas or benign pituitary adenoma).

   Note 1: A subject with any of the following conditions may be included in the study but requires prior approval from the Sponsor Medical Monitor:
   (a) > 10 microhemorrhages,
   (b) a focal area of superficial hemosiderosis > 1 cm,
   (c) prior hemorrhage > 1 cm^3
   (d) small vascular malformation, or
   (e) meningiomas ≥ 1 cm, or benign pituitary adenoma

   Note 2: For a subject who cannot undergo MRI, brain CT is acceptable but requires prior approval from Medical Monitor. CT showing significant pathology per the central reader, other than AD related findings, will be excluded.
   Note 3: CT is not allowed for subjects at sites in Germany.

2. Has a diagnosis of a neurodegenerative disorder other than AD.

3. Has been diagnosed with MDD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5), within one year prior to the Baseline Visit. A subject who does not meet criteria for MDD and who is on stable doses of antidepressants or mood stabilizers may be included in the study at the discretion of the Investigator.

4. Is currently taking memantine or has taken memantine within 12 weeks prior to the Baseline Visit.

5. Has a history of suicidal behavior within one year prior to the Baseline Visit; or has ongoing suicidal ideation with intent, with or without a specific plan or method (e.g., positive response to C-SSRS items 4 or 5 during the past 6 months).

6. Has a history of seizures, excluding febrile seizures of childhood or a single distant seizure (≥ 5 years rior to the Baseline Visit).

7. Has a medically confirmed history of recent cerebral infarct or transient ischemic attack within one year prior to the Baseline Visit.

8. Has a medically confirmed history of recent myocardial infarction or unstable, untreated coronary artery disease, or angina pectoris within 1 year prior to the Baseline Visit.

9. Has a lifetime history of schizophrenia, schizoaffective disorder, or bipolar disorder.

10. Has a history of, or currently has, any clinically significant ECG finding, or a QT interval corrected by Fridericia's method (QTcF) of > 450 msec for males and > 470 msec for females.
11. Has a history of cancer, diagnosed and treated within the last 3 years prior to the Baseline Visit, with the exception of the following: (a) treated basal cell carcinoma of the skin, (b) treated cutaneous squamous cell carcinoma in situ, (c) treated in situ or Stage 1 prostate cancer, (d) treated in situ cervical cancer, and (e) resected and cured early stage cutaneous melanoma (all require approval by the Sponsor's Medical Officer).
12. Has donated blood > 250 mL within 6 weeks prior to the Baseline Visit.
13. Has a history of alcohol or drug dependence or abuse according to the criteria of the DSM-5 within 2 years prior to the Baseline Visit.

    Note: A positive urine drug screen does not automatically exclude the subject, but requires review by Sponsor Medical Officer.
14. Has any significant medical condition or infection (e.g., uncontrolled cardiovascular, GI, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or other major disease or malignancy) that is unstable and that would either: (a) place the subject at undue risk from administration of study drug or from undergoing study procedures, or (b) interfere with the interpretation of safety or efficacy evaluations obtained in the course of the study.
15. Is unable to swallow ALZ-801 tablets or has a known intolerance or hypersensitivity to tramiprosate or any of the excipients contained in the ALZ-801 tablets.
16. Except when otherwise specified, has clinical laboratory tests outside normal limits per the laboratory's specification and considered clinically significant by the investigator at the Screening – Part 2 Visit.
17. Has clinically relevant abnormalities in serum thyroid-stimulating hormone (TSH) or calcium. If the subject is taking thyroid hormone replacement therapy, corresponding Screening test values must be considered not clinically significant by the investigator.
18. Has serum vitamin B_{12} below the lower limit of normal at the Screening – Part 2 Visit. A subject can be rescreened if he/she receives vitamin B_{12} treatment, and has a normal vitamin B_{12} level at least four weeks post-treatment.
19. Has any clinical chemistry laboratory value greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE; version 5.0; National Cancer Institute 2018) Grade 2, unless considered not clinically relevant by the Investigator.
20. Has one or more of the following at the Screening – Part 2 Visit:
    - Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN),
    - Aspartate aminotransferase (AST) > 3 × ULN, or
    - Total bilirubin (TBL) > 1.5 × ULN (except for subjects with diagnosed Gilbert syndrome with isolated hyperbilirubinemia).

21. Has an estimated glomerular filtration rate (eGFR) < 40 mL/min per 1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) formula [see National Institute of Diabetes and Digestive and Kidney Diseases website for formula MDRD formula for eGFR (SI units)].
22. Has a glycosylated hemoglobin (HbA1c) > 8% (National Glycohemoglobin Standardization Program) or 64 mmol/mol (International Federation of Clinical Chemistry) at the Screening – Part 2 Visit.
23. Only for subjects participating in the CSF sub-study: has impaired coagulation as determined by a prothrombin time (PT) according to the international normalized ratio (INR) > 1.5 or a platelet count < 50 × 10^9/L prior to CSF sampling.
24. Has a history of human immunodeficiency virus (HIV), or hepatitis B or C, or positive serology at the Screening – Part 2 Visit

    Note: Subjects with a history of hepatitis C who have been treated and cured (no detectable HCV RNA) are allowed.
25. Has participated in a clinical trial of any investigational drug, device, or experimental medication or intervention within 24 weeks prior to the Baseline Visit [Table 1].
26. Has participated in a clinical study and received active treatment with an anti-amyloid vaccine or an anti-tau vaccine [Table 1].
27. Has received any of the treatments listed in [Table 1] more recently than the indicated period prior to the Baseline Visit or plans to receive any of those during the study.
28. Anticipates receiving any of the treatment listed in [Table 1] during the current clinical study, or is currently participating in an ongoing clinical trial or plans to participate in a future clinical trial during the conduct of this study.

5.3. Prohibited Medications and Exceptions

Table 1 Prohibited Medications and Specified Washout Period

Prohibited Medications and Exceptions	Washout Period Before Baseline Visit (Visit 2)
Anti-amyloid or Anti-tau vaccine: Subjects who received active drug in a vaccine study are not eligible (subjects who received placebo are eligible)	Any use

Prohibited Medications and Exceptions	Washout Period Before Baseline Visit (Visit 2)
Potential disease modifying AD treatment: Subjects who received aducanumab treatment (US subjects) or who participated in a clinical study and received active drug: • Anti-amyloid or anti-tau antibodies (passive immunotherapy) • β-secretase or β-site amyloid precursor protein cleaving enzyme (BACE) inhibitors • Amyloid anti-aggregation agents • Anti-complement, anti-inflammatory, kinase inhibitors or other mechanisms	24 weeks
AChEI: Subject should remain on the same drug at the same dose during the study. **Exception:** During the study, down titration to a lower dose is allowed if necessary because of tolerability issues. This dose adjustment requires discussion with the Sponsor Medical Monitor.	Not applicable
Memantine: Memantine is not approved for subjects with MCI or Mild AD, and is not allowed in the study. Subjects requiring memantine after randomization must be withdrawn from the study.	12 weeks
Anti-parkinsonian medications: For example, L-dopa, amantadine, bromocriptine, pergolide, selegiline, I-deprenyl/selegiline, rasagiline). [Subjects with Parkinson's disease are excluded from the study.] **Exception:** carbidopa/levodopa and dopamine agonists are allowed for treating restless leg syndrome, but dose should be stable for at least 4 weeks prior to the Baselne Visit.	12 weeks
Oral Anticholinergic medications: Regularly used (> 3 doses/week) anticholinergic medications of ≥ moderate potency (e.g., benztropine, cyclobenzaprine, cyproheptadine, dicyclomine, diphenhydramine, promethazine, diphenoxylate with atropine, hydroxyzine, hyoscyamine, prochlorperazine, trihexyphenidyl, trimethobenzamide). [These drugs may interfere with cognitive assessments.]	4 weeks
Overactive Bladder medications: Oxybutynin. [The anticholinergic effect of this drug may interfere with cognitive assessments.] **Exception:** Daily use of the following medications are allowed: mirabegron, tolterodine, darifenacin, solifenacin, trospium, fesoterodine. Extended release formulations, where available, are preferred. Botulinum neurotoxin injection is allowed.	4 weeks

Prohibited Medications and Exceptions	Washout Period Before Baseline Visit (Visit 2)
Antidepressants: MAO inhibitors or antidepressants with ≥ moderate anticholinergic potency, including tricyclic antidepressants. Examples of prohibited antidepressants are: amitryptyline, amoxapine, clomipramine, desipramine, imipramine, isocarboxazide, maprotiline, nortriptyline, phenelzine, protriptyline, tranylcypromine, trimipramine. **Exception:** Use of antidepressants with < moderate anticholinergic potency such as SSRIs or SNRIs are acceptable if stable for at least 4 weeks before the Screening – Part 2 Visit **Examples of allowed antidepressants are:** citalopram, escitalopram, fluoxetine, paroxetine, sertraline, serotonin, duloxetine, venlafaxine, desvenlafaxine, trazodone, and mirtazapine.	4 weeks
Neuroleptics: Neuroleptics with ≥ moderate anticholinergic potency such as chlorpromazine, fluphenazine, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine, clozapine. **Exception:** Low doses of oral atypical antipsychotics are allowed, this includes • First generation drugs (olanzapine, quetiapine, risperidone, ziprasidone) • Second generation drugs (aripiprazole, asenapine, brexipiprazole, cariprazine, iloperidone, lurasidone and paliperidone)	4 weeks
Mood stabilizers and anticonvulsants: Lithium, valproic acid, phenytoin, levetiracetam, and carbamazepine. [These drugs may affect cognitive outcomes.] **Exception:** Use of pregabalin and gabapentin for neuropathic pain, and a stable low doses of zonisamide (≤ 100 mg/day) for pain, migraine, or sleep is acceptable.	4 weeks

Prohibited Medications and Exceptions	Washout Period Before Baseline Visit (Visit 2)
Sedatives/benzodiazepines: Regularly used (> 3 doses/week) sedatives/benzodiazepines (e.g., chlordiazepoxide, clonazepam, diazepam, meprobamate). [These drugs may interfere with cognitive assessments of clinical status.] **Exception:** Daily use of the following medications is acceptable if stable for at least 4 weeks before the Baseline Visit: • Hypnotic drugs used for insomnia, for example, zaleplon ≤ 5 mg, zopiclone ≤ 7.5mg, eszopiclone ≤ 3mg, ramelteon ≤ 8 mg, suvorexant ≤ 15 mg, and zolpidem ≤ 5 mg (or equivalent doses of same class) • Any as needed (prn) use ≤ 3 days per week • Short term use with > 3 doses/week is acceptable, even if tested positive for sedatives/benzodiazepines, may enter the study. Short term use is defined as ≤ 1 month. • Regular (> 3 days/week) use of low dose of sedatives/benzodiazepines, for example, lorazepam, temazepam, flurazepam, triazolam, estazolam, and quazepam (or equivalent doses of same class) allowed if stable for at least 4 weeks before the Baseline Visit after review by Sponsor Medical Officer • Regardless of sedatives/benzodiazepines usage, it is strongly recommended that subjects do not take these medications for at least 24 hours prior to cognitive assessments taken during clinic visits.	4 weeks
Analgesics/Narcotics: Regularly used (> 3 doses/week) narcotic analgesics (e.g., codeine, morphine, hydromorphone, oxycodone, propoxyphene and its variations, & combination products that contain a narcotic). [These drugs may interfere with cognitive assessments of clinical status.] **Exception:** Short term use (< 1 month) more than 3 doses/week is acceptable for temporary conditions. Narcotics are not to be used within 48 hours of cognitive testing at study visits.	4 weeks
Stimulant medications: For example, amphetamine, methylphenidate, atomoxetine, modafinil [These drugs may affect cognitive outcomes.]	4 weeks

Prohibited Medications and Exceptions	Washout Period Before Baseline Visit (Visit 2)
Anticoagulants: For example, warfarin, dabigatran, apixaban or other blood factor or thrombin inhibitor. [Increased risk of cerebrovascular events in APOE4/4 homozygotes carriers with potential cerebral amyloid angiopathy; anticoagulants also increase potential risks associated with LP.] **Exception:** Use of single anti-platelet therapy (e.g., aspirin or dipyridamole or clopidogrel) is permitted. Use of dual anti-platelet therapy (low-dose aspirin with dipyridamole or clopidogrel) is permitted. Subjects on dual anti-platelet therapy may be allowed to participate in the CSF sub-study after discussion with Sponsor Medical Monitor.	4 weeks
Corticosteroids: Systemic use: oral, intravenous, or intramuscular [These drugs may affect assessment of the neuroinflammatory biomarkers.] **Exceptions**: The following are acceptable: • Low dose oral treatment with the equivalent of ≤ 10mg prednisone • Short-term oral treatment with the equivalent of ≤ 60mg prednisone for < 4 weeks • Local injections into joints or bursae; topical, inhaled, or nasal use	4 weeks

BACE: β-secretase or β-site amyloid precursor protein cleaving enzyme; LP: lumbar puncture; MAO: monoamine oxidase; SNRI: serotonin and norepinephrine (noradrenaline) re-uptake inhibitors; SSRI: selective serotonin reuptake inhibitors.

Note: This is not a complete list of prohibited medications. Contact the Medical Monitor if there is a question about a specific medication.

5.4. Subject Identification and Allocation to Treatment

5.4.1. Subject Identification

Initials, year of birth, and age of subjects who have signed the ICF to begin Screening procedures will be collected in the source data for verification purpose. At Screening – Part 1 Visit, a unique identification number will be assigned by the interactive response technology (IRT). Any subject records or dataset that are transferred to the Sponsor will contain the identifier only; subject names, initials, date of birth, or any information which would make the subject identifiable will not be transferred.

In the rare circumstance where a subject is entered into the treatment part of the study, but does not receive the first dose of study drug, the Study Coordinator/Research Nurse must immediately inform the Clinical Research Associate (CRA) that the study drug was not administered.

5.4.2. Treatment Allocation

All subjects will be randomized to receive double-blind treatment consisting of either ALZ-801 265mg or placebo in a 1:1 ratio. Randomization will be stratified by use of concomitant AD medications (AChEI or none), age (50 through 65 years or > 65 years at the Screening – Part 1 Visit, gender, and disease stage (MMSE ≤ 26 or > 26 at the Baseline Visit). It is expected that

approximately 60% will be AD subjects with MMSE 22-26 (inclusive), and approximately 40% will be AD subjects with MMSE 27–30 (inclusive). Double-blind treatment will be dispensed in blister cards.

5.5. Subject Withdrawal, Termination, and Replacement

Study subjects may discontinue from the study or be withdrawn from the study for any of the following reasons:

- At the subject's or the subject's legally authorized representative with the subject's assent request for any reason (withdrawal of consent)
- Subject whose cognitive function declines and is deemed by the Investigator to be unable to provide assent/consent for continuation in the study
- At the discretion of the Investigator, if deemed appropriate, for any reason
- At the discretion of the Sponsor, if deemed appropriate, for any reason
- Subject for whom investigator deems initiation of memantine medically necessary must be withdrawn
- Subject noncompliance: If a subject takes less than 70% of study drug tablets, this may be considered reason for withdrawal, by Investigator or Sponsor request
- Protocol violation that compromises subject safety
- For safety concerns; medically significant AE(s) or SAE(s) with CTCAE > Grade 3 may be considered reason for withdrawal, if appropriate in the judgment of the Investigator
- Subject who becomes pregnant must be withdrawn from the study
- The subject's caregiver/study partner is no longer willing or able to participate in the study and a suitable replacement caregiver/study partner cannot be found
- Brain MRI findings: subject who has any of the following findings on central reading:
  - Macrohemorrhage: defined as hemorrhage with size > 1 cm^3
  - ARIA-E (vasogenic edema) associated with neurologic symptoms: dosing will be halted for 1 month and MRI repeated. Resumption of dosing may be considered after discussion between Investigator and Sponsor's medical officer.
- Subject who experiences an event of syncope without a clear triggering event (e.g., blood draw or pain inducing a vasovagal episode) will be withdrawn from the study
- Subject with clinically notable ECG abnormalities based on the average of triplicate ECG readings. The criteria for clinically notable or significant ECG results that require subject withdrawal are as follows:
  - QTcF (Fridericia's correction) interval > 500 msec, and
  - An increase in QTcF interval of > 60 msec from baseline.

Note: The criteria for QTcF are based on the upper threshold in elderly subjects who are known to have higher ULN [Reardon & Malik, 1996], and is the threshold commonly used in AD studies.

- Subject with confirmed clinically notable changes in liver function tests (LFT) may be withdrawn from the study. The criteria for abnormal LFTs are as follows:
  - ALT or AST > 8 × ULN,
  - ALT or AST > 5 × ULN for more than 2 weeks, or
  - ALT or AST > 3 × ULN, and TBL > 2 × ULN or PT > 1.5 × ULN
- Weight loss: Subjects who are not intentionally dieting who show the following degree of weight loss on study drug:
  - Weight loss > 6% of body weight compared to baseline, and
  - Reaching BMI < 22 if ≥ 65 years of age; or
  - Reaching BMI < 16 if < 65 years of age

  Note: The ideal body weight and BMI cut-off criteria for those < 65 years of age or ≥ 65 years of age are based on a meta-analysis by Winter et al. (2017).

The reason for discontinuation must be recorded on the appropriate page of the electronic case report form (eCRF).

Early Termination

Should a study subject request or decide to withdraw or is withdrawn by Investigator or Sponsor, an Early Termination (ET) Visit will be conducted at the time of discontinuation. All efforts should be made to conduct assessments and to complete and report observations as thoroughly as possible up to the date of withdrawal, including all the evaluations shown in the Schedule of Assessments [Appendix 2]. All information will be reported on the applicable pages of the eCRF.

If the subject withdraws from the study due to an AE, every reasonable attempt should be made to follow the subject until the AE resolves or until the Investigator, after discussion with the Sponsor, deems the AE to be chronic or stable. All SAEs will continue to be followed for 4 weeks after the ET visit or until the AE is deemed to be either chronic or stable.

Subject Replacement

If drop-out rate is more than projected (approximately 18%), subjects including those in the CSF sub-study who drop out may be replaced after discussion with the Safety Management Committee (SMC).

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1. Investigational Medicinal Product and Control Description

The investigational medicinal product (IMP) will be 265mg ALZ-801 (provided as 1 × 265mg tablets) or matching placebo (1 × placebo tablets [size- and color-matched to ALZ-801]).

All subjects will receive study drug, one tablet BID, taken with a morning and evening meal (or within 30 minutes after each meal) with approximately 10 to 12 hours between doses. Subjects in the placebo treatment arm will receive placebo tablets BID throughout the study. Subjects in the active treatment arm will receive placebo in the morning and a 265mg tablet of ALZ-801 in the evening during the first two weeks of the study; thereafter, they will receive a 265mg tablet BID.

On clinic visit days, only one dose of study drug will be taken from one of the newly dispensed blister cards and administered at the study site.

6.1.1. Formulation, Appearance, Packaging, Labeling, and Shipping

Formulation

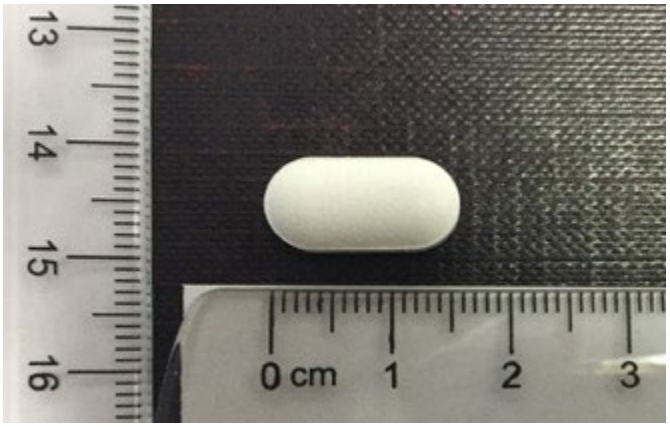
The ALZ-801 tablet consists of ALZ-801 drug substance, microcrystalline cellulose, silica colloidal anhydrous (Aerosil 200), PVP VA 64 (copovidone) and magnesium stearate. ALZ-801 tablets are coated with Opadry II White. Each tablet contains 265mg of ALZ-801 drug substance.

Placebo tablets contain all of the same excipients as ALZ-801 tablets, but do not contain any ALZ-801. ALZ-801 and placebo used for the tablets are manufactured under cGMP and meet specifications for clinical use.

Appearance

ALZ-801 is provided as white, oval-shaped, immediate release tablets [Figure 7].

Figure 7 Appearance of ALZ-801 and Matching Placebo Tablets



Packaging

ALZ-801 immediate-release tablets will be packaged as kits containing blister cards. Each blister card contains a 1-week supply with two blister strips, one for AM and one for PM dosing (8 tablets in each strip). The total number of tablets for a 1-week blister card is 16 tablets, for 7 days of dosing plus 1 day overage. The materials used for the blister strips are of standard commercial grade. The product contact side of this material conforms to FDA 21CFR175.300 and the Council of Europe Resolution AP (2004) and (EU) No. 10/2011.

Labeling

Representative label is shown below in [Figure 8].

Figure 8 Representative Label of Drug Product

ALZ-801 265 MG	**Protocol code: ALZ-801-AD301**
FOR CLINICAL TRIAL USE ONLY Each blister card contains a 1-week supply with two blister strips (8 tablets in each strip) for AM and PM dosage of ALZ-801 immediate release tablets or placebo. The total number of tablets for a 1-week blister card is 16 tablets. **Kit Number:** **Site Number:** **Batch Number:** **Patient Number:** **Investigator**: **Date of dispensation:** **Expiry date: MMM/YYYY** **Dosing schedule:** Orally, twice per day, approximately 10-12 hours apart. Tablets shall be taken with a full meal or within 30 minutes after a full meal. On clinic visit days, only one dose of study drug will be taken from one of the newly dispensed blister cards and administered at the study site. Use only according to study physician's instructions. **Store at room temperature (15-25 °C).** **Caution: NEW DRUG- Limited by Federal (U.S.A.) law to investigational use only.** **KEEP OUT OF REACH OF CHILDREN.** **Sponsor**: Alzheon, Inc., 111 Speen Street, Suite 306, Framingham, MA 01701, USA; Tel.: +1-508-861-7709.	

Shipping

Study drug will be shipped directly to the pharmacist or study coordinator/research nurse at the study site after all required regulatory and legal documents have been received by the Sponsor or its designee. Upon receipt of the study drug shipment, the pharmacist or study coordinator/research nurse will verify the condition of the study supplies, register the study drug, and document per instructions provided.

Instructions for resupply shipments or replacement of study drug are provided in the IRT Manual.

6.1.2. Product Storage and Stability

IMP must be stored in a limited access area at room temperature (15°C to 25°C or 59°F to 77°F). Only authorized study personnel may access the study drug according to local and national regulations.

6.1.3. Replacement Procedures for Investigational Medicinal Product

Instructions to resupply shipments or replacement of study drug are provided in the IRT Manual.

6.2. Dosing and Administration, and Adjustment

6.2.1. Dosing Regimen

Study drug will be administered as an oral tablet beginning at the Baseline Visit (Day 1). The first dose of study drug will be administered in the clinic and must be administered to the study subject **only after** all pre-dose assessments (including the blood draw) are performed.

The dosing regimen is one tablet orally BID except on clinic days when one tablet only will be administered at the study site. In the initial 2-week titration period, the active treatment group will receive placebo in the morning and ALZ-801 in the evening. Thereafter, ALZ-801 will be administered in the morning and evening. In the placebo group, subjects will always receive placebo in the morning and evening throughout the study. The last dose of study drug will be administered at the clinic on the morning of the Week 78 visit.

The study drug should be taken with a full meal or within 30 minutes after a full meal (breakfast or dinner) with approximately 10 to 12 hours between doses. On days of clinic visits, dosing of study drug for the day will occur once and will be administered by the site staff at the site. The times of study drug administration the night prior to clinic visit and when taken at the study site will be recorded.

6.2.2. Dose Adjustments/Modifications/Delays

Dosage adjustments or down titration will not be allowed for ALZ-801 throughout the study except for the dose change on Day 15 after the titration period.

No gradual reduction in medication is required for withdrawal from the study. If for any reason, a subject misses one or more doses of study drug, he/she should resume the regular dosing regimen, unless informed otherwise. The interruption in study drug dosing should be reported and recorded.

6.3. Study Drug Accountability

It is the responsibility of the Investigator to supervise accurate monitoring of the receipt, storage, dispensing, and accounting of all study drug according to accepted medical and pharmaceutical practice. Copies of all shipment records of study drug shipments must be retained. Accurate, original site records of study drug inventory and dispensing must be maintained using the forms provided or using the form the site pharmacy maintains, if they are approved for use by the Sponsor or designee.

All study drug documentation must be maintained by the Pharmacist or dispenser. All disposition records must be made available for inspection by the Sponsor or their designee, upon request.

Drug accountability forms will be provided for the accounting of study drug at the subject level and for the overall study inventory. A reason(s) must be provided for any tablets that are not accounted for.

Only subjects enrolled in the study may receive study drug and only authorized study site personnel may supply or administer the drug. Only study drug with appropriate expiry dates may be dispensed.

Study subjects will be instructed to return all dispensed study drug blister cards to the study site at each visit. Blister cards dispensed at the previous visit will be collected, and the Pharmacist or

designee at the site will inspect all returned blister cards, as well as record the number of used and unused tablets on the drug accountability log. Each site must keep all used and unused blister cards until the CRA either arranges return to the distribution center or gives instruction for their disposal. If unused tablets remain at the end of the study, they will be accounted for at the site close-out visit in the presence of the CRA, who will provide instructions for study drug disposal.

6.4. Study Drug Compliance

All subjects in this study will commence therapy onsite on Day 1 (Baseline); oral study drug will be administered under clinic staff supervision. After subjects are discharged to continue therapy at home, subjects and their caregivers/study partners should be counseled on the need to meet 100% compliance with study drug. The Investigator or designee should ensure that subjects meet this goal throughout the study period. Compliance will be assessed on subsequent visits by returned tablet count. Administration of investigational product and any deviation(s) from the prescribed dosage regimen should be recorded.

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Specific Procedures/Evaluations

All study procedures and evaluations will be completed according to the Schedule of Assessments as shown in [Appendix 2]. Every effort should be made to complete the required procedures and evaluations at the designated visits and times.

7.1.1. Remote Visits

Coronavirus disease 2019 (COVID-19) has significantly impacted study subjects' ability to attend study visits due to government-ordered lockdowns or the closure of state (domestic) and/or national borders and may continue to do so.

Protocol deviations, urgent safety measures, and modifications to this protocol might be necessary to prioritize and ensure the safety of trial participants, their families, and study site teams, and maintain the integrity of the study. All measures and actions that may be implemented due to COVID-19 will be reviewed by the Data and Safety Monitoring Board (DSMB), Medical Monitor, and applicable Principal Investigators.

For any skipped in-person visits based on the availability of the patient/ the study team, within approximately ± 3 days of the originally scheduled visit, the study team should contact the subject (and as applicable, their caregiver/study partner/legal representative) via phone/telemedicine to collect information in order to monitor AEs or SAEs, and provide study oversight (hereafter referred to as "remote visits").

Protocol deviations related to COVID-19 will be documented. These deviations in protocol-specific procedures due to COVID-19 (changes in study visit schedules, remote and/or missed visits, or patient discontinuations) may lead to missing information.

For each patient, the eCRF will capture specific information that (as much as possible) explains the basis of the missing data, including the relationship to COVID-19 for missing

protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19).

7.1.2. Informed Consent

At Screening – Part 1 Visit, prior to stated procedures (APOE genotyping, MMSE, demographics, medical history and prohibited medications) are performed, the site staff will obtain the signed ICF from each subject or the subject's legally authorized representative with the subject's assent. Complete signed ICF from subject and caregiver/study partner will be obtained prior to any other procedures at the Screening – Part 2 Visit or at the Screening – Part 1 Visit if APOE4/4 status is known or confirmed using a rapid genotype test.

7.1.3. Prohibited Medications

The list of prohibited medications starting at the Screening – Part 1 Visit and at all times during the study is provided in [Table 1].

7.1.4. Permitted Medications

During the study, any concomitant medications deemed appropriate by the Investigator to treat the subject's medical condition may be prescribed, excluding those that are prohibited. Refer to [Table 1], which also lists the exceptions to prohibited medications.

Change in dose of any permitted medications during the study period is discouraged.

All concomitant medication usage will be recorded during each study visit.

7.1.5. APOE Genotyping

A blood sample for APOE genotyping will be required at the Screening – Part 1 Visit as shown in the Schedule of Assessments [Appendix 2]. Previous evidence of APOE4/4 status may be used as a reference and allow subjects to combine Screening – Part 1 Visit and Screening – Part 2 Visit together at the same day if the site and subject prefer.

Result from the central laboratory blood test of APOE4/4 status must be available prior to randomization.

The blood sample may be stored, with subject consent, for possible future analysis with core AD-related biomarkers, such as p-tau$_{217}$, Aβ40, and Aβ42 as well as NfL and GFAP. Consent for use of this sample for possible future analysis with core AD-related biomarkers is optional.

7.1.6. Future Potential Genomic Testing

A blood sample for future potential genomic testing will be requested at the Screening – Part 2 Visit as shown in the Schedule of Assessments [Appendix 2]. Consent for the collection and use of this sample is not required for study participation.

7.1.7. Subject Demographics and Medical History

At the Screening – Part 1 Visit, the subject's demographics and medical history will be obtained. The demographics should include, but not be limited to, age, race, ethnicity, and gender. The medical history should include, but will not be limited to, the subject's clinically significant and relevant medical history of the following body systems: head, eyes, ears, nose, and throat;

neurological; endocrine; dermatological; cardiovascular; respiratory; GI; genitourinary; musculoskeletal; hematological; hepatic; renal; and immunological systems.

7.1.8. Prior and Concomitant Medications

Prior medications and past treatment(s) taken within the last 24 weeks prior to the Baseline Visit, as well as ongoing medications taken before the administration of the first dose of study drug, will be recorded.

A concomitant medication is defined as any medication that is taken after administration of the first dose of study drug (i.e., after receiving study drug at the Baseline Visit). Any use of concomitant medications will be recorded. During the study, initiation of or change in concomitant medications to treat an AE will also be recorded.

7.1.9. Subject Eligibility

At both the Screening – Part 2 and Baseline Visits (prior to dosing), the site staff will be responsible for reviewing the inclusion and exclusion criteria to determine the subject's eligibility for the study.

7.1.10. Safety Assessments

7.1.10.1. Assessment of Adverse Events

AEs will be recorded beginning after signing the ICF at the Screening – Part 1 Visit until completion of the study or the final Follow-up Visit, whichever is later. AEs will be evaluated by the Investigator for severity (using CTCAE version 5.0; National Cancer Institute 2018), seriousness, and attributability to study medication. Further details on AEs, including definitions, elicitation, and reporting are provided in [Section 8].

AEs that occur before receiving study drug at the Baseline Visit will be captured as non-treatment emergent AEs. Treatment-Emergent AEs are those that occur anytime after subject has received first dose of study drug at the Baseline Visit and until the end of the Safety follow up visit or the Early Termination Visit.

7.1.10.2. Physical Examination

Complete physical examination will be conducted at the scheduled visits prior to dosing shown in the Schedule of Assessments [Appendix 2].

7.1.10.3. Neurological Examination

Neurological examination will be conducted at the scheduled visits prior to dosing shown in the Schedule of Assessments [Appendix 2]. The neurological examination should include level of consciousness, speech, cranial nerves [including pupil equality and reactivity], motor assessment, sensory assessment, coordination, gait, reflexes, and Romberg test.

7.1.10.4. Height and Weight Measurements

Height will be collected at the Screening – Part 2 Visit only. Weight measurement will be taken at the Screening – Part 2 Visit and at all post treatment clinic visits as shown in the Schedule of Assessments [Appendix 2].

7.1.10.5. Vital Signs

Vital sign measurements (blood pressure [BP], pulse, respiratory rate, and body temperature) will occur prior to dosing, lumbar puncture (LP), and blood draw, where applicable. BP and pulse will be measured after the subject is sitting for at least 5 minutes. All BP measurements should be performed in the same arm while sitting, preferably by the same person with an inflatable cuff and a calibrated manometer. Vital signs will be taken at the scheduled visits shown in the Schedule of Assessments [Appendix 2].

After the last blood collection in a visit, subjects will be observed for approximately 15 minutes. BP and pulse will be measured and documented at the end of this observation period.

7.1.10.6. Brain Imaging

Brain MRI scans will be scheduled and performed within the window specified for each visit shown in the Schedule of Assessments [Appendix 2].

The screening MRI report per central reader will be used to determine study eligibility, by excluding other neuropathologies, and as baseline for volumetric assessment of the imaging biomarkers. Post dose MRI will be used for safety monitoring and for volumetric MRI assessment of the imaging biomarkers.

MRIs will be performed using either 1.5 or 3 Tesla scanners. Details of the MRI sequences are described in the MRI study manual.

Sedation is permitted for claustrophobic subjects who have difficulty tolerating the MRI procedure according to local standard procedures. For those who cannot undergo MRI, CT is acceptable at Screening but requires prior approval by Medical Monitor. These subjects will not be scheduled for further CT imaging and will not contribute to the assessment of the volumetric imaging biomarkers. CT is not allowed for subjects at sites in Germany.

7.1.10.7. Electrocardiogram

ECGs will be performed as shown in the Schedule of Assessments [Appendix 2]. A standard triplicate 12-lead ECG will be performed at the Screening – Part 2 Visit, Week 6, and Week 13. At subsequent visits, a single 12-lead ECG will be performed unless there is evidence of QT prolongation previously or in or current visit, in which case a triplicate ECG must be performed. The ECG should be obtained after the subject has rested in a supine position for at least 5 minutes. This assessment may be performed any time before blood sampling or at least 30 min after blood sampling, if applicable.

ECG intervals (e.g., interval representing the time for both ventricular depolarization and repolarization to occur [QT interval], QTcF interval, interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization [QRS duration], and time from the onset of the P wave to the start of the QRS complex [PR interval]) and any clinically significant findings will be recorded. The tracings will be reviewed and reported by the central ECG reader.

7.1.10.8. Columbia-Suicide Severity Rating Scale

The C-SSRS will be performed prior to dosing to assess suicide risk at the visits shown in the Schedule of Assessments [Appendix 2].

7.1.10.9. Safety Laboratory Assessments

Safety laboratory tests are summarized in [Table 2]. Clinical chemistry, hematology, coagulation tests, and urinalysis will be performed in all subjects at the scheduled visits shown in the Schedule of Assessments [Appendix 2]. At each visit, blood tests will be done after the completion of all study procedures except for study drug dosing and dispensing.

Table 2 Clinical Laboratory Tests

Panel/Assessments	Visits	Parameters to be Analyzed
Genotyping (Blood)	Screening – Part 1 only	APOE genotype
Immunology	Screening – Part 2 only	HIV-1/-2 Ag and Ab Hep B S Ag Hep C Ab HCV RNA (if applicable)
Clinical Chemistry	Screening – Part 2 only	HbA1c Vitamin B12 TSH FSH (all females of non-childbearing potential only) hCG (all females of childbearing potential only)
Clinical Chemistry	Screening – Part 2, Weeks 6, 13, 26, 39, 52, 65, 78, and ET	Albumin ALP AST ALT GGT TBL Direct bilirubin Indirect bilirubin Lactate dehydrogenase Blood urea nitrogen Creatinine* Glucose Magnesium Potassium Sodium Total protein Calcium Chloride Phosphorus Uric acid
Hematology	Screening – Part 2, Weeks 6, 13, 26, 39, 52, 65, 78, and ET	Hemoglobin Hematocrit RBC count RBC MCV White blood cell count with differential (percentage of neutrophils, lymphocytes, monocytes, eosinophils, basophils) Platelet count
Coagulation Tests	Screening – Part 2, Weeks 6, 13, 26, 39, 52, 65, 78, and ET	aPTT PT INR for PT
Urinalysis	Screening – Part 2, Weeks 6, 13, 26, 52, 78, and ET	Color Appearance pH Specific gravity Glucose Protein Ketones Blood Microscopic examination (RBC, white blood cells, epithelial cells, casts, crystals, bacteria) Urine pregnancy test (all females of child bearing potential only) at all visits except Screening – Part 2

ALT: alanine aminotransferase; ALP: alkaline phosphatase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; ET: early termination; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; HbA1c: glycosylated hemoglobin; hCG: human chorionic gonadotropin; HCV RNA: hepatitis C virus RNA; Hep B S Ag: hepatitis B surface antigen; Hep C Ab: hepatitis C antibody; HIV: human immunodeficiency virus; INR: International normalized ratio; MCV: mean corpuscular volume; PT: prothrombin time; RBC: red blood cells; TBL: total bilirubin; TSH: thyroid-stimulating hormone

* Used to calculate glomerular filtration rate according to the Modification of Diet in Renal Disease formula.

It is preferred that urine samples for urinalysis and other urine testing is collected at the first void performed at the clinic. All clinical laboratory samples and urine samples for urinalysis will be analyzed at a central laboratory. The urine pregnancy test, if applicable, will be analyzed at the study site.

All laboratory reports must be reviewed, initialed, and dated by the Principal Investigator or by a Sub-Investigator who is a physician or other qualified health care professional involved in the study conduct at the site. Each abnormal test will be evaluated as clinically significant or not clinically significant. All clinically significant abnormal laboratory values that represent an unexpected CBL should be assessed as AEs, and an AE eCRF must be completed. Any clinically significant abnormal values that persist should be followed until they have been resolved or the Investigator, in consultation with the Medical Monitor, assesses them to be chronic or stable.

7.1.10.10. Serum FSH or hCG Test

Serum FSH levels will be measured only for female subjects of non-childbearing potential at the Screening – Part 2 Visit. Serum human chorionic gonadotropin (hCG) levels will be measured only for female subjects of childbearing potential at the Screening – Part 2 Visit.

Serum FSH levels for female subjects of non-childbearing potential should be in the postmenopausal range as determined by the laboratory for study entry. Serum hCG levels for female subjects of childbearing potential must indicate negative pregnancy results for study entry.

7.1.10.11. Urine Pregnancy Test

Urine pregnancy test will be performed at subsequent visits prior to dosing shown in the Schedule of Assessments [Appendix 2] for females of childbearing potential. Pregnancy tests must be negative to continue the study.

7.1.10.12. Urine Drug Screen

Urine drug screen will be performed at the Screening – Part 2 Visit as shown in the Schedule of Assessments [Appendix 2]. Drugs of abuse to be screened for include amphetamines, MDMA, barbiturates, benzodiazepines, cannabinoids, cocaine, phencyclidine, ethanol, and opiates.

Subjects who use cannabidiol (CBD) oil must commit to withholding consumption for at least 24 hours prior to all clinic visits.

7.1.10.13. Screens for HIV and Hepatitis B and C

HIV antigen and antibody, hepatitis B surface antigen (Hep B S Ag), and hepatitis C antibody (Hep C Ab) and HCV RNA (if applicable) tests will be conducted at the Screening – Part 2 Visit as shown in the Schedule of Assessments [Appendix 2].

7.1.11. Clinical Efficacy Assessments

All clinical efficacy assessments will be collected on electronic tablets and will be considered source data. In the uncommon event that a tablet is not functional, assessments will be collected on paper and considered as the source data, and will be entered into the tablet later.

7.1.11.1. Alzheimer's Disease Assessment Scale – Cognitive Subscale

The ADAS-Cog is a brief neuropsychological assessment used to assess the severity of cognitive symptoms. The ADAS-Cog 13 consist of 13 questions including word recall task, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition task, remembering test directions, spoken language, comprehension, word-finding difficulty, delayed word recall, and digit cancellation tasks. The total test score ranges from 0 to 85. The worse the cognition (cumulative number of errors), the greater the score.

The ADAS-Cog 11 includes all of above items except for delayed word recall and digit cancellation tasks with a total score ranging from 0 to 70.

The ADAS-Cog will be administered, while audio-recorded, to the subject by properly certified site staff at the visits shown in the Schedule of Assessments [Appendix 2]. It is highly recommended that the same rater for a given subject perform the ADAS-Cog throughout the study.

7.1.11.2. Amsterdam Instrumental Activities of Daily Living

The A-IADL Questionnaire is a 70-item informant-based computerized questionnaire aimed at detecting deficits in complex functions at the early stages of AD [Sikkes et al. 2013]. It will be assessed at the visits shown in the Schedule of Assessments [Appendix 2]. Instrumental ADL can be described as the activities necessary to function independently in society. These activities include, but are not limited to, cooking, doing finances, and shopping. They are complex everyday tasks, determined by multiple cognitive processes and controlled processing. They can be distinguished from basic ADL, which include basic self-care skills.

7.1.11.3. Disability Assessment for Dementia

The DAD evaluates the basic and instrumental activities in daily activities of subjects with dementia. The proxy-respondent scale specifically measures daily living tasks in terms of executive functions.

A 40-item scale is part of the DAD, which addresses a range of functional domains: eating, meal preparation, telephoning, hygienic, dressing, medication, corresponding, finance, leisure, and housework.

The DAD will be administered to the subject by properly qualified and trained site staff at the visits shown in the Schedule of Assessments [Appendix 2].

7.1.11.4. Clinical Dementia Rating – Global Score and Sum of Boxes

The CDR is a global rating scale used to assess the stage and severity of dementia. It uses a structured, clinician-rated interview that collects information on cognitive and functional capacity from both the subject and caregiver, on performance in six areas (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Each of the six areas (boxes) is rated on a scale of 0, 0.5, 1, 2, or 3 where 0 is normal, 0.5 is *Questionable* and 3 is *Severe*. The scores of each of the areas are added together to determine the Sum of Boxes (SB) score. The CDR-SB is used as measurement of efficacy response. A Global Score will also be calculated.

The CDR will be administered by qualified and trained raters at the site during the Screening – Part 2 Visit to determine eligibility for entry into the study based on the global score, and at the visits shown in the Schedule of Assessments [Appendix 2].

It is important to ensure that a CDR rater is not influenced by knowledge of the ADAS-cog and/or MMSE scores. Therefore, for a given subject, the interview-based CDR should be administered by one rater, while the ADAS-Cog and/or MMSE should be administered by a different rater at the Screening – Part 2 Visit and beyond.

- A CDR rater should not access the ADAS-cog and/or MMSE scores before administering the CDR interview.
- For each subject, it is highly recommended that the CDR rater remains the same throughout the study period.
- A CDR rater may administer clinical scales except for ADAS-cog and MMSE.
- A CDR rater may have access to other clinical data except for ADAS-cog and MMSE.
- A rater may be assigned to administer the CDR for one subject and be assigned to perform the ADAS-cog and/or MMSE for another subject.

7.1.11.5. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) – Delayed Memory Index Score

The RBANS identifies and characterizes abnormal cognitive decline in older adults and serves as a screening battery for younger subjects [Randolph et al. 1998]. The entire battery yields scaled scores for five cognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The Delayed Memory domain includes List Recall, List Recognition, Story Memory, and Figure Recall.

The Delayed Memory test will be administered by qualified and trained raters at the site during the Screening – Part 2 Visit [Appendix 2]. The Delayed Memory Index Score will serve to determine eligibility for study enrollment.

7.1.11.6. Mini-Mental State Examination

The MMSE is a brief cognitive test assessing general cognitive function that has been used in numerous clinical studies of FDA products approved for the treatment of AD. It will be administered by qualified and trained raters at the site at the visits shown in the Schedule of Assessments [Appendix 2]. MMSE at the Screening – Part 1 Visit can be performed by any qualified rater, while at the Baseline Visit and beyond, the same rater for a given subject is preferred throughout.

The MMSE score from the Screening – Part 1 Visit serves to assess subject eligibility for the study. The MMSE score from the Baseline Visit is used to stratify eligible subjects in the study. The MMSE will also be used as an exploratory measure of efficacy.

7.1.11.7. Neuropsychiatric Inventory

The NPI 12-item form is designed to be a self-administered questionnaire completed by caregivers about subjects for whom they care. Each of the 12 NPI domains contains a survey question that

reflects cardinal symptoms of that domain. Initial responses to each domain question are "Yes" (present) or "No" (absent). If the response to the domain question is "No", the informant goes to the next question. If "Yes", the informant then rates both the Severity of the symptoms present within the last month on a 3-point scale and the associated impact of the symptom manifestations on them (i.e., Caregiver Distress) using a 5-point scale. The NPI provides symptom Severity and Distress ratings for each symptom reported, and total Severity and Distress scores reflecting the sum of individual domain scores.

The NPI will be administered to the subject by properly qualified and trained site staff at the visits shown in the Schedule of Assessments [Appendix 2].

7.1.11.8. Quality of Life in Alzheimer's Disease

The QoL-AD is a 13-item questionnaire designed to provide both subject and caregiver or study partner report of the QoL for subjects with AD. The 15-item QoL-AD includes an additional four items, including the ability to take care of oneself, live with others, make own life choices, and people who work within the residential setting.

The QoL-AD will be administered to the subject and caregiver or study partner by properly qualified and trained site staff at the visits shown in the Schedule of Assessments [Appendix 2].

7.1.11.9. Resource Utilization in Dementia

The RUD Lite consists of two sections: one about the caregiver (including questions about the caregiver, and time spent caring for the subject), and the other one about the subject (including questions about the subject's living arrangements and their healthcare resource usage).

The RUD Lite will be administered to the subject by properly qualified and trained site staff at the visits shown in the Schedule of Assessments [Appendix 2].

7.1.12. Biomarker Assessments

7.1.12.1. Cerebrospinal Fluid Biomarkers

The CSF sub-study will enroll approximately 120 subjects (60 per group). Subjects who participate in the CSF sub-study will undergo an LP according to the site's standard procedures [Appendix 2]. For each subject, all 3 LPs should be performed within a 2-hour time window. For example, if the first LP occurs at 10 AM and the second LP occurs at 12 PM, the third LP must occur between 10 AM and 12 PM. If the first LP occurs at 10 AM and the second LP occurs at 8 AM, the third LP must occur between 8 AM and 10 AM. The actual date and time of CSF collection (not time of preparation) will be recorded. LPs should be performed via gravity drip method with atraumatic needles to reduce the risk of CSF leakage and post-LP headaches. This technique will allow for optimal biomarker collection and analysis. Further details about CSF biomarker sampling are provided in the Laboratory Manual.

Assays will evaluate the effects of study drug on the following CSF biomarkers: p-tau$_{181}$, p-tau$_{217}$, Aβ40, Aβ42, NfL, t-tau, neurogranin, sTREM2, YKL-40, and GFAP.

Other potential additional analyses of CSF biomarkers of importance in AD, such as Aβ oligomer assay, may be evaluated when assays become available.

7.1.12.2. Plasma Biomarkers

Plasma biomarker samples will be collected at the visits shown in the Schedule of Assessments [Appendix 2]. For each subject, sampling for plasma biomarkers should be performed within the same 2-hour time window on each of the clinic visits regardless of dosing time and other assessments. The actual date and time of each sample will be recorded.

The approximate amount of blood to be withdrawn is shown in [Table 3]. Further details about the handling, storage and transport of all samples will be specified in the Laboratory Manual.

Assays will evaluate the effects of study drug on the following plasma biomarkers: p-tau$_{181}$, p-tau$_{217}$, Aβ40, Aβ42, NfL, and GFAP.

Other potential additional analyses of plasma biomarkers of importance in AD may be evaluated when assays become available.

7.1.12.3. Imaging Biomarkers

All Subjects will undergo vMRI to evaluate the effects of ALZ-801 on hippocampal volume, cortical thickness, and whole brain volume at the visits shown in the Schedule of Assessments [Appendix 2].

The actual date and time of the vMRI will be recorded. Further details about vMRI are provided in the MRI Study Manual.

7.1.13. Pharmacokinetic Assessments

Plasma PK samples will be collected at pre-dose at the visits shown in the Schedule of Assessments [Appendix 2]. Additionally, a PK sample at ≥ 1 hour post-dose during clinic visit should be collected at Week 65. The actual date and time of each sample will be recorded. The times of study drug administration that occurred the night prior to clinic visit and when taken at the study site will be recorded.

The amount of blood to be withdrawn for PK sampling is shown in [Table 3]. Further details about plasma PK sampling are provided in the Laboratory Manual.

CSF PK samples will be taken when CSF biomarker samples are collected from the subjects who participate in the CSF sub-study at the visits shown in the Schedule of Assessments [Appendix 2]. The actual date and time of CSF collection (not time of preparation) will be recorded. Further details about CSF PK sampling are provided in the Laboratory Manual.

If a subject inadvertently takes the morning ALZ-801 dose prior to the clinic visit, a PK sample should still be drawn at the clinic, and the sampling and dosing times will be recorded.

Plasma samples will be used to evaluate the PK of ALZ-801, tramiprosate, and its metabolite 3-SPA in all study subjects. CSF samples will be used to evaluate CSF drug levels from subjects in the CSF sub-study. All sample collection, processing, storage and shipping instructions are provided in the Laboratory Manual.

7.1.14. Total Volume of Blood Collection

The total volume of blood collection for each subject will vary depending on the duration of study treatment and central laboratory requirements. At any time during the study, if any laboratory

abnormalities are found for a subject, additional blood may be drawn for safety monitoring. [Appendix 2].

For subjects who complete the study, the total blood volume collected over 52 weeks will be approximately 210 mL, and over 78 weeks will be approximately 270 mL. The approximate total blood volume to be drawn at each visit is shown in [Table 3].

Table 3 Approximate Blood Volume to be Drawn at Each Study Visit

Time Point	Chemistry Creatinine FSH/hCG TSH B12	Chemistry Creatinine	Hem.	Coagulation (PT, INR, aPTT)	APOE Genotype	Future Potential Genomic Testing	Immunology (HIV, Hep B S Ag, Hep C Ab, HCV RNA if applicable)	Plasma Biomarkers	PK	Total Per Visit
Screening – Part 1	—	—	—	—	9 mL	—	—	—	—	9 mL
Screening – Part 2	4 mL	—	3 mL	3 mL	—	9 mL	6 mL 4 mL	—	—	29 mL
Baseline	—	—	—	—	—	—	—	16 mL	4 mL	20 mL
Week 6	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL	30 mL
Week 13	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL	30 mL
Week 26	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL	30 mL
Week 39	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL	30 mL
Week 52	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL	30 mL
Week 65	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL×2	34 mL
Week 78	—	4 mL	3 mL	3 mL	—	—	—	16 mL	4 mL	30 mL
Safety Follow-up at Week 82	—	—	—	—	—	—	—	—	—	—
		Total Blood Volume per Subject over 52 Weeks: 208 mL **Total Blood Volume per Subject over 78 Weeks: 272 mL**								

aPTT: activated partial thromboplastin time; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HCV RNA: hepatitis C virus RNA; Hep B S Ag: hepatitis B surface antigen; Hep C Ab: hepatitis C antibody; Hem: hematology; HIV: human immunodeficiency virus; INR: International normalized ratio; PK: pharmacokinetics; PT: prothrombin time; TSH: thyroid-stimulating hormone

7.1.15. COVID-19 Related Special Consideration

7.1.15.1. COVID-19 Infection

If a subject contracts COVID-19 anytime during the study, he/she can start/resume study procedures (includes screening and study visits) after fulfilling required criteria per local guidelines.

7.1.15.2. COVID-19 Vaccination

If a subject receives a COVID-19 vaccine at anytime during the study (after signing the ICF), he/she may remain in the study provided that the in-clinic assessment occurs at least six weeks

after the first vaccine dose or at least two weeks after the last (including booster) vaccine dose, as applicable.

7.2. Procedures by Visit

The study procedures for each visit are shown in the Schedule of Assessments [Appendix 2].

7.2.1. Screening – Part 1 Visit – (Up to 13 weeks prior to Baseline Visit)

Screening – Part 1 Visit will be conducted to determine eligibility status based on MMSE score, APOE genotype, prohibited medications, and demographics, and medical history to determine initial eligibility of the subject, and to schedule MRI for those subjects who qualify (except for APOE genotype if not known yet) based on these criteria.

Previous evidence of APOE4/4 status may be used as a reference and allow the Screening – Part 1 and Screening – Part 2 Visits to occur together at the same day if preferable. Alternatively, screening procedures may be conducted over several visits provided that the results are available to evaluate inclusion and exclusion criteria before randomization.

The following procedures should be performed in this order:

- Informed consent for the Screening – Part 1 Visit from subject (or the subject's legally authorized representative with the subject's assent)

  Note: Signed and dated informed consent for the Screening – Part 1 Visit must be obtained before any study procedures listed below are perfrormed.
- Demographics, medical history
- MMSE
- Blood sample for APOE genotype testing
- Prohibited medications
- Note: Any untoward medical event that occurs after signing the initial ICF will be recorded as an AE.

If a subject fails the Screening – Part 1 Visit, one re-screening is allowed. Any additional re-screening (Screening – Part 1) requires sponsor approval.

7.2.2. Screening – Part 2 Visit

Eligible subjects after the Screening – Part 1 Visit will enter the Screening – Part 2 Visit. Procedures may be conducted over several visits during the Screening period provided that the results are available before randomization.

The following procedures will be performed. The recommended order is shown below:

- Informed consent from subject (or the subject's legally authorized representative with the subject's assent) and caregiver/study partner

  Note: Signed and dated informed consent for the Screening – Part 2 Visit must be obtained before any study procedures listed below are perfrormed.

- Vital signs (prior to blood draw), and BP and pulse approximately 15 minutes after last blood draw
- Physical examination
- Neurological examination
- Height
- Weight
- AE assessment
- Prior medications taken within 24 weeks prior to the Baseline Visit and all current medications
- RBANS
- CDR
- C-SSRS
- AD diagnostic criteria
- Evidence of progressive memory loss over the last 12 months per investigator assessment as captured on the diagnostic verification form
- Triplicate 12-lead ECG
- Safety laboratory tests: clinical chemistry, hematology, and coagulation
- Serum FSH/hCG test
- Serum immunology screens for HIV and hepatitis B and C
- Blood sample for future potential genomic testing
- Urine for urinalysis
- Urine for drug screen
- MRI: For subjects with acceptable screening tests performed as above, MRI will be scheduled prior to Baseline Visit.

If a subject fails the Screening – Part 2 Visit, one re-screening is allowed. Any additional re-screening (Screening – Part 2) requires sponsor approval. If a subject fails screening due to RBANS Delayed Memory score, the subject may be re-screened after discussion with the Sponsor.

7.2.3. Visit 2 – Baseline Visit (Day 1)

The following procedures will be performed. The recommended order is shown below:

- Inclusion/exclusion criteria
- Vital signs (prior to blood draw)
- Physical examination
- Weight

- AE assessment
- All medications taken since last visit (whether currently being taken or discontinued)
- ADAS-Cog
- MMSE
- A-IADL
- DAD
- NPI
- QoL-AD
- RUD Lite
- C-SSRS
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine pregnancy test (female subjects of childbearing potential)
- Randomization to treatment
- Study drug dosing (exact time of dosing will be recorded). The first dose of study drug must be administered only after all the above assessments have been completed. Except on clinic visits when the study drug will be administered at the site, the subject will be instructed to start taking the study drug BID with morning and evening meals (or within 30 minutes after each meal) with approximately 10 to 12 hours between doses.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- BP and pulse approximately 15 minutes after last blood draw

For subjects in the CSF sub-study:

- Site may schedule the LP up to 10 days prior to the Baseline Visit.
- LPs should be performed via gravity drip method with atraumatic needles to reduce the risk of CSF leakage and post-LP headaches. This technique will allow for optimal biomarker collection and analysis.
- Pre-dose CSF sample collection for biomarker assessment (exact time will be recorded)
- Pre-dose CSF sample collection for PK assessment (exact time will be recorded)

7.2.4. Visit 3 (Phone) – Week 2 (Day 15 ± 2 days)

The following items will be assessed via a telephone call 2 weeks after the Baseline Visit (Day 1). Ideally, the contact is made directly with the subject himself or herself; the caregiver/study partner may provide information to support the subject's self-report.

- AE assessment
- Change in medications since last visit

7.2.5. Visit 4 – Week 6 (Day 43 ± 7 days)

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Weight
- AE assessment
- Change in medications since last visit
- C-SSRS
- Triplicate 12-lead ECG
- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine for urinalysis
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- BP and pulse approximately 15 minutes after last blood draw

7.2.6. Visit 5 – Week 13 (Day 92 ± 14 days)

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination

- Weight
- AE assessment
- Change in medications since last visit
- ADAS-Cog
- MMSE
- C-SSRS
- Triplicate 12-lead ECG
- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine for urinalysis
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance.
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- BP and pulse approximately 15 minutes after last blood draw

7.2.7. Visit 6 (Phone) – Week 20 (Day 141 ± 2 days)

The following items will be assessed via a telephone call 7 weeks after Visit 5. Ideally, the contact is made directly with the subject himself or herself; the caregiver/study partner may provide information to support the subject's self-report.

- AE assessment
- Change in medications since last visit

7.2.8. Visit 7 – Week 26 (Day 183 ± 14 days)

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Neurological examination
- Weight

- AE assessment
- Change in medications since last visit
- ADAS-Cog
- MMSE
- A-IADL
- CDR
- DAD
- NPI
- C-SSRS
- Single 12-lead ECG (triplicate if corrected QT [QTc] prolongation observed previously or in current visit)
- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine for urinalysis
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- BP and pulse approximately 15 minutes after last blood draw
- MRI (within the visit window)

7.2.9. Visit 8 – Week 39 (Day 274 ± 14 days)

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Weight
- AE assessment
- Change in medications since last visit

- MMSE
- C-SSRS
- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- BP and pulse approximately 15 minutes after last blood draw

7.2.10. Visit 9 – Week 52 (Day 365 ± 14 days)

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Neurological examination
- Weight
- AE assessment
- Change in medications since last visit
- ADAS-Cog
- MMSE
- A-IADL
- CDR
- DAD
- NPI
- QoL-AD
- RUD Lite
- C-SSRS

- Single 12-lead ECG (triplicate if QTc prolongation observed previously or in current visit)
- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine for urinalysis
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- BP and pulse approximately 15 minutes after last blood draw
- MRI (within the visit window)

For subjects in the CSF sub-study:

- MRI should be performed and results available prior to LP.
- LPs should be performed via gravity drip method with atraumatic needles to reduce the risk of CSF leakage and post-LP headaches. This technique will allow for optimal biomarker collection and analysis.
- Site may schedule the LP ± 14 days of the window specified.
- Pre-dose CSF sample collection for biomarker assessment (exact time will be recorded)
- Pre-dose CSF sample collection for PK assessment (exact time will be recorded)

7.2.11. Visit 10 – Week 65 (Day 456 ± 14 days)

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Weight
- AE assessment
- Change in medications since last visit
- MMSE
- C-SSRS

- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- Study drug dispensing
- One post-dose plasma PK sample at ≥ 1 hour post-dose (exact time will be recorded)
- BP and pulse approximately 15 minutes after last blood draw

7.2.12. Visit 11 – Week 78 (Day 547 ± 14 days) [End of Treatment]

Week 78 visit is considered the end of treatment (EOT) visit. The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Neurological examination
- Weight
- AE assessment
- Change in medications since last visit
- ADAS-Cog
- MMSE
- A-IADL
- CDR
- DAD
- NPI
- QoL-AD
- RUD Lite
- C-SSRS
- Single 12-lead ECG (triplicate if QTc prolongation observed previously or in current visit)

- Safety laboratory tests
- Pre-dose plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Pre-dose plasma sample collection for PK assessment (exact time will be recorded)
- Urine for urinalysis
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug return, accountability, and compliance
- Study drug dosing (morning only). Exact times of dosing that occurred the night prior to clinic visit and during clinic visit will be recorded. The subject will be instructed not to take an evening dose on the day of the clinic visit.

  Note: Study drug dosing will not occur until all of study procedures listd above are perfrormed.
- BP and pulse approximately 15 minutes after last blood draw
- MRI (within the visit window)I

For subjects in the CSF sub-study:

- MRI should be performed and results available prior to LP.
- LPs should be performed via gravity drip method with atraumatic needles to reduce the risk of CSF leakage and post-LP headaches. This technique will allow for optimal biomarker collection and analysis.
- Site may schedule the LP ± 14 days of the window specified.
- Pre-dose CSF sample collection for biomarker assessment (exact time will be recorded)
- Pre-dose CSF sample collection for PK assessment (exact time will be recorded)

7.2.13. Safety Follow-up Visit – Week 82 (Day 574 ± 7 days) [End of Study]

The Safety Follow-up Visit is considered the end of study (EOS). It will occur approximately 4 weeks after the Week 78 visit. The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Neurological examination
- Weight
- AE assessment
- Change in medications since last visit
- C-SSRS

7.2.14. Early Termination Visit

Early Termination is also considered an EOT visit. An ET Visit should be completed if a study subject discontinues prematurely from the study, or is discontinued from the study by the Investigator [see Section 5.5].

If a study subject prematurely discontinues from study treatment, an ET Visit should be conducted at the time of discontinuation. Every effort should be made to conduct all ET procedures as specified below and in the Schedule of Assessments [Appendix 2]. Every attempt should be made to follow study subjects who have an SAE for 4 weeks after their ET Visit. For subjects who continue to be followed for safety, SAEs should continue to be reported as described in [Section 8.4.2].

The following procedures will be performed. The recommended order is shown below:

- Vital signs (prior to blood draw)
- Physical examination
- Neurological examination
- Weight
- AE assessment
- Change in medications since last visit
- ADAS-Cog
- MMSE
- A-IADL
- CDR
- DAD
- NPI
- QoL-AD
- RUD Lite
- C-SSRS
- Single 12-lead ECG (triplicate if QTc prolongation observed previously or in current visit)
- Safety laboratory tests
- Plasma sample collection for biomarker assessment (exact time of sampling will be recorded)
- Plasma sample collection for PK assessment (exact time will be recorded)
- Urine for urinalysis
- Urine pregnancy test (female subjects of childbearing potential)
- Study drug dosing from the last dose prior to the visit (time of dosing will be recorded)

- Study drug return, accountability, and compliance
- BP and pulse approximately 15 minutes after last blood draw
- MRI (as soon as possible, no later than 2 weeks after the ET visit)

For subjects in the CSF sub-study:

- MRI should be performed and results available prior to LP.
- LPs should be performed via gravity drip method with atraumatic needles to reduce the risk of CSF leakage and post-LP headaches. This technique will allow for optimal biomarker collection and analysis.
- Site should schedule the LP as soon as possible, no later than 2 weeks after the MRI.
- CSF sample collection for biomarker assessment (exact time will be recorded)
- CSF sample collection for PK assessment (exact time will be recorded)

7.2.15. Retrieved Dropout Visit

In addition to the ET visit, subjects who discontinue the study drug during the trial will be encouraged to remain in the study (off study drug) for continued RDO visits by attending Week 52 (if applicable) and Week 78 (EOT) visits. The RDO visits will include the following procedures, in the recommended order shown below:

- Vital signs
- AE assessment
- Change in medications since last visit
- ADAS-Cog
- A-IADL
- MMSE
- NPI

For subjects who prematurely withdraw from the study,, they will be encouraged to return at Week 78 to finish study-related procedures.

7.2.16. Unscheduled Visit

Unscheduled Visit, at the discretion of the Investigator, may occur at any time, and appropriate procedures and evaluations will be conducted and documented in the eCRF.

8. ADVERSE EVENTS

8.1. Specification of Safety Parameters

All of the following safety endpoints will be recorded on the eCRF.

- Occurrence and severity of TEAEs and SAEs

- Occurrence of clinically significant abnormal findings in laboratory tests, as determined by the Investigator
- Occurrence of clinically significant abnormal findings in ECG, as determined by the central ECG reader
- Occurrence of abnormal findings in physical examination, including weight and vital signs (pulse rate, body temperature, respiratory rate, and BP)
- Occurrence of abnormal findings in MRI central readings for ARIA-E or ARIA-H
- Occurrence of abnormal findings in C-SSRS
- Pregnancy for females of childbearing potential

8.1.1. Definition of Adverse Event (AE)

Adverse Event: An AE is any untoward medical event that occurs in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. Examples include the following:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the subject's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder]);
- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity, or toxicity to study drug;
- Apparently unrelated illnesses;
- Injury or accidents;
- Exacerbations of the underlying disease (indication);
- Extensions or exacerbations of symptomatology, subjective events reported by the study subject, new clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination.

The following is not considered an AE:

- Elective procedure unless related to the AD diagnosis
- Pre-existing conditions found as a result of screening procedures

Treatment-emergent Adverse Event: A TEAE is defined as any new AE that begins, or any preexisting condition that worsens in severity, after at least one dose of study treatment has been administered.

8.1.2. Definition of Serious Adverse Event (SAE)

Serious Adverse Event: An SAE is defined as any untoward medical event that results in any of the following outcomes:

- Death
- A life-threatening AE

  Note: This means that the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically may have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization
  - Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization. Hospitalization may include social hospitalization, defined as inadequate family support or care at the study subject's primary residence that results in the study subject being admitted to the hospital (i.e., wound care, nutrition).
  - Exceptions: Emergency Room visits that do not result in a hospital admission; outpatient surgery; preplanned or elective procedures; and/or protocol procedures. These events would not be reported as SAEs unless the event triggering the hospital visit is an SAE as defined by other SAE criteria such as life-threatening, resulting in disability or incapacity, or per the medical judgment of the Investigator.
  - Any other event fulfilling the definition of serious that develops as a result of the in-hospital procedure or extends the hospital stay is an SAE.
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
  - Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.
- A congenital anomaly or birth defect
- Important medical event(s)
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Pregnancy: In addition, and for the purposes of monitoring, the following should be reported via the Pregnancy eCRFs, as appropriate, according to the instructions provided in [Section 8.4.3].

- Any occurrence of pregnancy of female study subjects or female sexual partners of male study subjects (with or without AEs).
- Any study subject who becomes pregnant during the study must be withdrawn from treatment and will be followed to term and/or other pregnancy outcome.
- For all female study subjects, a serum pregnancy test must be performed at the Screening – Part 2 Visit.

- Females of non-childbearing potential are defined as follows:
  - Be postmenopausal with amenorrhea for at least 1 year prior to the first dose and FSH serum levels consistent with postmenopausal status, or
  - Have undergone one of the following documented sterilization procedures at least 6 months prior to the first dose:
    - hysteroscopic sterilization,
    - bilateral tubal ligation or bilateral salpingectomy,
    - hysterectomy, or
    - bilateral oophorectomy.
- Females of childbearing potential, defined as a premenopausal female capable of becoming pregnant, will be included if they are either sexually inactive (sexually abstinent for 14 days prior to the first dose and confirm to continue through 28 days after the last dose) or using one of the following highly effective contraceptives (i.e., results in < 1% failure rate when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose:
  - IUD,
  - surgical sterilization of the partner (vasectomy for 6 months minimum),
  - combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal),
  - progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable),
  - IUS, or
  - bilateral tubal occlusion.

8.1.3. Definition of Unanticipated Problems

The Office of Human Research Protection (OHRP) considers unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and ICF; and (b) the characteristics of the participant population being studied
- Related to participation in the research
- Research placing participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

This study will use the OHRP definition of UPs.

8.2. Classification of an Adverse Event

8.2.1. Severity of Event

Investigators should assess the severity of AEs according to the National Cancer Institute CTCAE version 5.0. In general, CTCAE severity grades are defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

These five categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the study subject's reports, the physician's observations, and the physician's prior experience. The severity of the AE should be recorded in the appropriate section of the eCRF. The evaluation of severity is distinguished from the evaluation of "seriousness." A severe event may not meet the criteria for seriousness and a serious event may be evaluated as mild.

8.2.2. Causality

The following should be considered when assessing causality:

- temporal associations between the agent and the event;
- cessation or rechallenge;
- compatibility with known class effect;
- known effects of concomitant medications;
- pre-existing risk factors;
- a plausible mechanism; and
- concurrent illnesses.

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

Categories of attribution for "Related"

- Definitely related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

- Possibly related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the study subject's clinical condition, other concomitant events).

Categories of attribution for "Unrelated"

- Unlikely to be related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event.
- Not related: An AE will be considered "not related" to the use of the product if any of the following tests are met:
  - An unreasonable temporal relationship exists between administration of the product and the onset of the AE (e.g., the event occurred either before or too long after administration of the product for it to be considered product related).
  - A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident).
  - A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event).

8.2.3. Expectedness

Sponsor will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described in the Investigator's Brochure.

8.3. Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, dates and times of onset and resolution, clinician's assessment of severity, assessment of relatedness to study drug (assessed only by those with the training and authority to make a diagnosis), and action taken. All AEs occurring while on study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator or designee will record all reportable events with start dates occurring any time after informed consent is obtained until the AE has resolved, stabilized, or a new chronic baseline has been established. At each study visit, the Investigator or designee will inquire about the

occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4. Collecting, Reporting, and Recording Procedures

8.4.1. Collecting, Reporting, and Recording Adverse Events

All AEs will be collected and recorded in the eCRF for each subject from the day of signed ICF until the end of Safety Follow-up Visit. All AEs regardless of relatedness to the study drug, must be fully and completely documented on the AE eCRF and in the subject's medical notes. AEs may be volunteered spontaneously by the study subject or discovered by the study staff during physical and neurological examinations or by asking an open-ended non-leading question such as: "How have you been feeling since you were last asked?" The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure. All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, stabilized, or a new chronic baseline has been established, abnormal laboratory values have returned to baseline or normal levels, there is a satisfactory explanation for the changes observed, the subject is lost to follow-up, or the subject has died.

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom.

Concomitant illnesses that existed before entry into the study will not be considered an AE unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page as well as on the SAE Report Form (Medical History section).

8.4.2. Collecting, Reporting, and Recording Serious Adverse Events

In addition to the severity rating, each AE is to be classified by the Investigator as "serious" or "not serious." The seriousness of an event is defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the criteria listed in [Section 8.2.1].

The reporting of SAEs by the Sponsor to the Regulatory Authorities is a regulatory requirement. Each Regulatory Authority has established a timetable for reporting SAEs based upon established criteria. It is the responsibility of the principal Investigator to report to the Pharmacovigilance and Safety Services group and to document the SAE in the eCRF within 24 hours of learning of occurrence.

The SAE (initial and/or follow-up) must be reported by completing the SAE eCRFs, as appropriate (refer to the eCRF Completion Guidelines for details). Calls related to fatal/life-threatening SAEs should first be directed to the Medical Monitor (refer to the contact list in this protocol for contact information). If the Medical Monitor is not available, please contact the Sponsor Medical Officer.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is the term used to refer to a serious adverse event that occurs in a clinical trial subject, which is assessed by the Sponsor as being unexpected and having a reasonable possibility of a causal relationship with the study drug (adverse reaction). Reports of these reactions are subject to expedited submission to health authorities.

SAEs are to be reported via the electronic data capture (EDC) system when it is available the SAE eCRFs are to be completed with all the current information (refer to the eCRF Completion Guidelines for details).

If the EDC system is unavailable, SAEs can be reported on a paper form. This form (for initial and/or follow-up information) and cover sheet will include all available supporting documentation relevant to the event. This form is to be emailed (within 24 hours of discovery) to the following:

SAE REPORTING CONTACT INFORMATION

Department: Pharmacovigilance and Safety Services

Company: [redacted]

Email address: [redacted]

Telephone: [redacted]

Fax: [redacted]

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits and phone contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. In the event of any SAE (other than death), the study subject will be instructed to contact the Investigator (or designee) using the telephone number provided in the ICF. All study subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

All SAEs will continue to be followed until the end of the study or until such events have resolved or the Investigator, in conjunction with the Sponsor, deems them to be chronic or stable.

SAEs occurring up to the safety follow-up visit should be reported.

8.4.3. Collecting, Reporting, and Recording Pregnancy

Females of childbearing potential will be required to take pregnancy test before IMP administration. The results of the pregnancy testing must be negative in order to be in the study.

- Females of non-childbearing potential are defined as follows:
  - Be postmenopausal with amenorrhea for at least 1 year prior to the first dose and FSH serum levels consistent with postmenopausal status, or
  - Have undergone one of the following documented sterilization procedures at least 6 months prior to the first dose:
    - hysteroscopic sterilization,
    - bilateral tubal ligation or bilateral salpingectomy,

  - hysterectomy, or
  - bilateral oophorectomy.

- Females of childbearing potential, defined as a premenopausal female capable of becoming pregnant, will be included if they are either sexually inactive (sexually abstinent for 14 days prior to the first dose and confirm to continue through 28 days after the last dose) or using one of the following highly effective contraceptives (i.e., results in < 1% failure rate when used consistently and correctly) 14 days prior to the first dose continuing through 28 days after the last dose:
  - IUD,
  - surgical sterilization of the partner (vasectomy for 6 months minimum),
  - combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal),
  - progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable),
  - IUS, or
  - bilateral tubal occlusion.

In the event that a female subject or a male subject whose female partner does become pregnant at any time through 28 days after the last dose, the Investigator must notify the Medical Monitor or designee within 48 hours of learning about the pregnancy. Any study subject that becomes pregnant during the study must be withdrawn from treatment and will be followed to term and/or other pregnancy outcome.

The Investigator will be required to complete the Pregnancy Report/Outcome Form and any additional documents provided by the Sponsor, follow the subject through the pregnancy term, and report to the Medical Monitor or designee the course of the pregnancy, including perinatal or neonatal outcome.

Information on the status of the mother and the child will be forwarded to the Medical Monitor or designee using the Pregnancy Report/Outcome Form. Any premature termination of the pregnancy will also be reported on this form.

Although pregnancy occurring in a clinical study is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and will be followed as such. A spontaneous abortion is considered to be an SAE.

8.5. Safety Oversight

This study will have an independent DSMB to oversee subject safety and well-being as detailed in [Section 13.5]. In addition, the Study SMC consisting of the Sponsor and contract research organization personnel will regularly monitor all aspects of subject safety throughout this study, including but not limited to all SAEs, AEs, clinical laboratory data, ECG data, MRI, weight loss, and other relevant safety data such as physical examination findings. The Study SMC will meet at regular intervals, but no less than monthly to review the emerging safety data. The details of the

safety reviews and composition of the SMC will be detailed in the Safety Management Plan and the SMC charter, respectively.

9. CLINICAL MONITORING AND COMPLIANCE

9.1. Study Monitoring

Monitoring procedures approved by the Sponsor will be followed in order to comply with GCP guidelines. Remote and on-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits, whenever possible, from a representative of the Sponsor who will review the eCRFs and source documents. This CRA will be qualified by training, education and experience to monitor the progress of sites participating in a clinical study and to ensure that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP and the applicable regulatory requirements.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study. Source data verification (SDV) is an essential part of the monitoring process and the Investigator must grant direct access to the original subject's source documents. The extent and nature of monitoring will be described in detail in the monitoring plan.

In the event of pandemics, alternative monitoring measures may be required if on-site monitoring is not permitted and deviations to the study monitoring schedule are necessary. If it is not possible to follow the recommended monitoring schedule of onsite visits due to national, local, or site-specific restrictions, possible temporary, alternative measures may be implemented to maintain proper oversight of the clinical trials. All monitoring deviations related to the pandemic should be well-documented to enable appropriate evaluation of the clinical trials.

Remote SDV will be allowed if the site and Principal Investigator agree to this method of monitoring due to pandemic restrictions for onsite monitoring visits. To facilitate remote SDV, scans of source document worksheets, assessment forms, and other required documentation will be sent to the monitor. Monitors should be trained on remote SDV procedures. No protected health information should be scanned and sent to the monitors. If a site allows the monitors to have access to their electronic medical records, this should only be available to the monitor during the time of the remote visit. Site staff should be available to respond to monitors questions during the remote monitoring visit.

9.2. Data Quality Assurance

The Sponsor's representatives and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data), provided that subject confidentiality is respected.

The Study Monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify the following: adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The CRA should

have access to study subject medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator must agree to cooperate with the CRA to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for an audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records may occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

9.3. Audits and Inspections

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.4. Archiving Study Documents

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 15 years following the completion of the study. ICFs and adequate records for the receipt and disposition of all study drug must be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA and other applicable Regulatory Authorities are notified, unless a longer period is required by applicable law or regulation. The Investigator must not discard any records unless given written authorization by the Sponsor.

Investigators are responsible for all study records and the accuracy of the subject data and source documents. It is required that Investigators contact the Sponsor or its designee for the following:

- If the study files are relocated to another facility or the custodian of the records is changed at any time while the records are being stored.
- If the Investigator delegates responsibility for these documents to another person.

Subject identity information will be maintained for 15 years unless applicable law or regulation requires a longer period.

10. STATISTICAL METHODS AND DATA ANALYSIS

10.1. General Considerations

All statistical processing will be performed using the most current version of SAS® at the time of the analysis. Data summaries and listings will be provided for all baseline variables collected (subject disposition, all demographic and baseline characteristics, prior and concomitant medications, and study drug compliance), all efficacy outcomes, all safety outcomes (deaths, AEs, clinical laboratory values, vital signs, ECG assessments, physical examination, and neurological examination), all fluid and imaging biomarker outcomes, and CSF and plasma concentrations of

ALZ-801, tramiprosate, and 3-SPA. Individual data will be listed and sorted by treatment, subject ID, visit, and time point.

Summary statistics for continuous measurements will be reported using the number of study subjects with data values, mean, median, standard deviation (SD), minimum, and maximum. For continuous efficacy outcomes 95% confidence intervals will be provided.

Summary statistics for categorical variables will be reported using the number and percentage of study subjects within each level of the variable.

Baseline values for a given variable are defined as the last values collected prior to the first administration of ALZ-801.

A detailed SAP will be developed and finalized prior to the final database lock, and submitted to regulatory authorities per local guidelines. Any analyses after database lock that represent deviations from the final approved SAP will be described and justified in the clinical study report.

10.2. Endpoints for Statistical Considerations

See Section 4.2 for endpoints for statistical considerations.

10.3. Determination of Sample Size

10.3.1. Primary Clinical Outcome

The total study sample size will be approximately 300 subjects or 150 subjects per treatment group (TRT). The sample size was determined based on efficacy data from an AD study with tramiprosate, the active agent in ALZ-801. These efficacy data were observed with tramiprosate 150mg BID, which provides plasma exposures similar to ALZ-801 at 265mg BID, the dose used in this study. In the previous 78-week AD study, the APOE4/4 subpopulation treated with tramiprosate showed approximately 5.0 point difference from placebo (benefit) on ADAS-Cog 11 in Mild AD subjects with baseline MMSE scores of 22-26 [Abushakra et al. 2017].

For the primary efficacy outcome of ADAS-Cog 13, this study is powered to detect a 3.0 point difference between ALZ-801 and placebo in the CBL to Week 78. This assumes a within-treatment SD of approximately 8.1 in the drug arm and 5.6 in the placebo arm.

A sample size of 125 subjects per arm will provide approximately 90% power to show a 3-point difference between the two treatment groups at a significance level of $\alpha = 0.05$ (2-sided). The drop-out rate is estimated to be approximately 17% at 78 weeks, thus a total of 300 subjects enrolled would provide approximately 250 completers or approximately 125 per arm.

10.3.2. Fluid Biomarker Outcome

CSF Sub-study: For CSF p-tau$_{181}$, the primary fluid biomarker outcome, sample size determination was based on data from two Early AD studies with anti-amyloid antibodies that showed significant (13% to 17%) reduction in CSF p-tau over 78 weeks [Tolar et al. 2020b]. We therefore assumed the following:

- Expected baseline mean CSF p-tau$_{181}$ level in each study arm : 90 to 110 pg/mL

- CSF p-tau$_{181}$ levels at week 78 are expected to be approximately 15% lower than baseline in the ALZ-801 arm and to remain stable in the placebo arm, with approximately 15% difference in CBL between ALZ-801 and placebo
- Expected difference: $\Delta = 15$ pg/mL
- Confidence level: $1-\alpha = 95\%$
- 2-sided test on paired samples

A sample size of 45 subjects per arm provides > 90% power to detect a delta of 15 pg/mL (decrease) in CSF p-tau$_{181}$ at 78 weeks, assuming a SD of 25 pg/mL; and provides power of approximately 90% assuming a SD of 30 pg/mL. A total of 60 subjects enrolled would provide approximately 48 completers per arm, assuming 20 % drop out rate in the CSF sub-study.

For plasma p-tau$_{181}$, it is assumed that the difference in CBL between ALZ-801 and placebo CBL will be similar to CSF, namely a 15% difference. A sample size of 125 completers per arm is therefore expected to provide > 90% power.

10.3.3. Imaging Biomarker Outcome

For total hippocampal volume, the power calculation is based on the assumption that the placebo arm experiences hippocampal atrophy of 6% while the drug arm experiences approximately 4% atrophy over 78 weeks. The baseline hippocampal volume is assumed to be approximately 3100 mm^3, the delta is expected to be 68 mm^3, with SD of 165 mm^3 and 147 mm^3 for the drug arm and placebo arms, respectively. A sample size of 125 per arm provides > 90% power to detect a 40% attenuation in hippocampal atrophy compared to placebo at 78 weeks, at a significance level of $\alpha = 0.05$ (2-sided).

10.4. Subject Stratification

Randomization will be stratified by use of concomitant AD medications (AChEI or none), age (50 through 65 years or > 65 years at the Screening – Part 1 Visit), gender, and disease stage (MMSE ≤ 26 or > 26 at the Baseline Visit). It is expected that approximately 60% will be AD subjects with MMSE 22-26 (inclusive), and approximately 40% will be AD subjects with MMSE 27–30 (inclusive).

10.5. Study Populations

The criteria for study populations are described below and in the SAP. A subject classification document will be prepared and signed before database lock.

10.5.1. Safety Population

The Safety population will include all study subjects who received at least one dose of study drug. All safety analyses will be conducted on this population.

10.5.2. Modified Intent-to-Treat Population (mITT)

The mITT population will include all study subjects who have received at least one dose of study drug, have one baseline assessment, and have also completed at least one scheduled post-baseline

visit with at least one valid post baseline efficacy assessment. All primary and secondary efficacy analyses will be conducted on this population.

10.5.3. Per Protocol Population (PPP)

The PPP will include all study subjects who have completed the study and who are at least 80% compliant with study drug for the duration of their study participation. The PPP will be used for sensitivity analyses of the primary and secondary efficacy endpoints.

10.5.4. Completer Population (CP)

The CP will include all randomized subjects who receive at least one dose of study drug, being on treatment until Week 78 and have completed the study, regardless of compliance with study drug. Subjects who discontinue treatment prematurely will not be included in this population even if they adhere to the scheduled visits. The CP will be used for sensitivity analyses of the primary and secondary efficacy endpoints.

10.5.5. Pharmacokinetic Population

The PK population will include all treatment assigned study subjects who have received at least one dose of active treatment and have at least one evaluable post-dose PK sample.

10.5.6. Populations for Exploratory Analyses

Populations for exploratory analyses will be described in the SAP.

10.6. Demographics, Baseline Characteristics, and Other Background Information

10.6.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized overall, by the two categories of disease severity, and by region (North America and Europe).

10.6.2. Prior and Concomitant Medications

All prior and concomitant medications will be listed and summarized by anatomical therapeutic chemical classification levels 2 and 4. The number and percentage of subjects who are on drugs that could affect behavior and cognition will be summarized.

10.6.3. Subject Disposition

The number and percentage of study subjects who discontinue will be reported overall and by reason for discontinuation.

10.6.4. Study Drug Compliance

Study drug compliance will be listed.

10.7. Efficacy Analyses

10.7.1. Hierarchical Hypothesis Testing

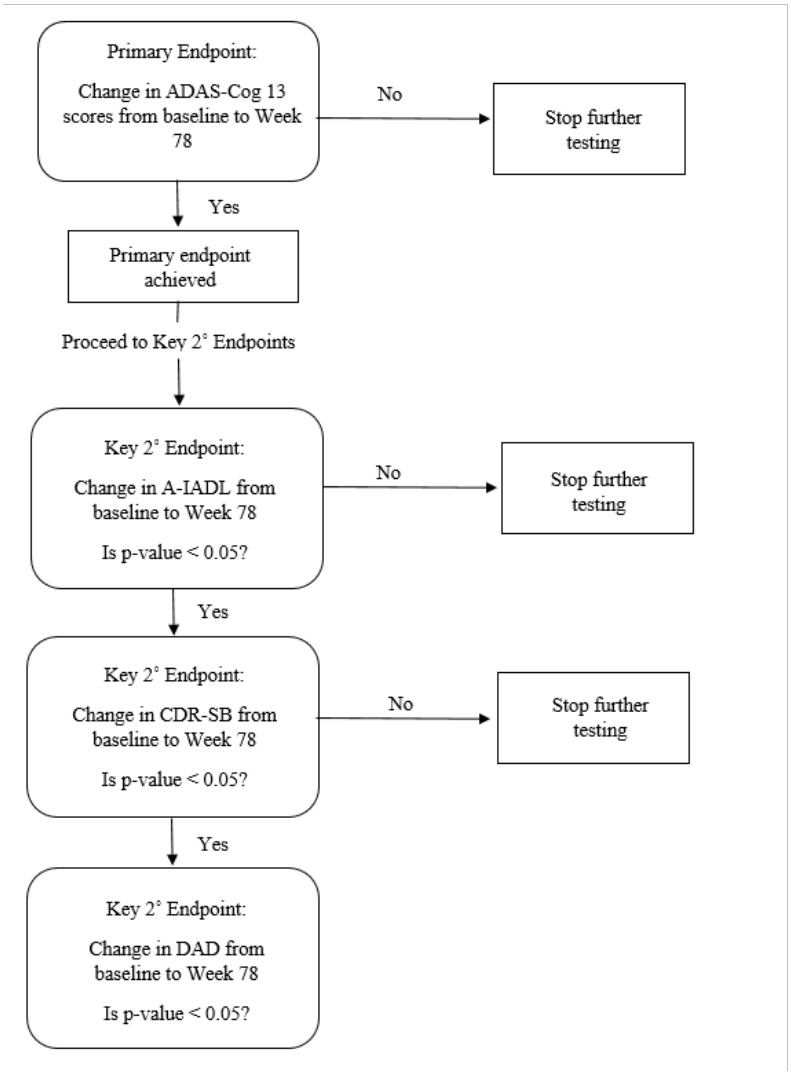
A fixed sequence hierarchical testing approach will be used to test multiple endpoints in a predefined order to control the family-wise type 1 errors arising from multiple comparisons. Only after a success on the testing of the previous endpoint will the next endpoint be tested.

If the primary endpoint is significant at the 0.05 significance level, the key secondary endpoints will be analyzed using a fixed-sequence step-down procedure to control for multiplicity in the secondary endpoints. The three key secondary endpoints (CBL to week 78 in A-IADL, CDR and DAD) will be tested in sequential order at significance levels of 0.05. The order of testing will be A-IADL, followed by CDR-SB, followed by DAD [Figure 9]. The hypothesis testing for the additional clinical endpoints will be considered exploratory.

The order of the hierarchical tests is:

1. Primary efficacy endpoint: CBL to Week 78 in ADAS-Cog 13
2. Key secondary endpoint: CBL to Week 78 in A-IADL
3. Key secondary endpoint: CBL to Week 78 in CDR-SB
4. Key secondary endpoint: CBL to Week 78 in DAD

Figure 9 Hierarchical Testing Process in Study ALZ-801-AD301



ADAS-Cog 13: 13-item Alzheimer's Disease Assessment Scale – cognitive subscale; A-IADL: Amsterdam Instrumental Activities of Daily Living; CDR-SB: Clinical Dementia Rating – Sum of Boxes; DAD: Disability Assessment for Dementia

10.7.2. Primary Efficacy Analysis

Unless otherwise specified, all primary efficacy analyses will be performed using the mITT population. Analyses of the primary endpoint of ADAS-Cog 13 will be performed with a likelihood based linear MMRM on treatment observed case (OC) data. The OC data set will consist of actual observations recorded at each visit during the double-blind treatment period and no missing data will be imputed. The model terms will include treatment, the stratification factors of use of concomitant AD medications (AChEI or none), age group (50 through 65 years or > 65 at the Screening – Part 1 Visit), gender, disease severity based on MMSE at the Baseline Visit, baseline ADAS-Cog 13 values, visit (VISIT), and treatment by visit interaction. The visit variable will be used to define the within-subject repeated measures over time. The least squares mean (LSM) for each treatment at each visit will be generated together with its 95% confidence interval, and the LSM difference between the active treatment and placebo will also be calculated; together

with its standard error, and the 2-sided 95% confidence interval. For the primary endpoint at 78 weeks, treatment comparisons will be done at the 0.05 significance level.

All data collected during the study will be used in the statistical analysis. Additional details will be described in the final SAP. Sensitivity testing of the primary endpoint will include MMRM analyses for the PPP, and the CP.

For subjects who discontinue treatment prior to trial completion, every attempt will be made to have them continue with clinic visits and study assessments. Particular attention will be given to collecting Week 78 ADAS-Cog 13 assessments, regardless of when subjects discontinued treatment. These data from retrieved dropouts data will be used to impute missing data using multiple imputation method as a sensitivity analysis for the primary endpoint. This method assumes that the best reflection of what happened to the early dropout patients at Week 78 are the retrieved dropouts. For those subjects who terminate treatment prematurely but have Week 78 assessments, and the intermediate missing off-treatment data will be imputed by interpolation for analyses.

10.7.3. Secondary Endpoint Analyses

The same MMRM method applied to the primary efficacy endpoint will be used to evaluate the between-treatment difference for the key secondary endpoints. No explicit missing data imputation will be performed except for that which is inherent in the MMRM. Differences between treatments, the p-values, and the 2-sided 95% CIs will be calculated within the framework of MMRM.

Note that only the post-baseline visits on which the endpoints are scheduled to be measured will be included in the model. The secondary endpoint analyses will be analyzed using the mITT population, PPP, and CP.

All other secondary efficacy endpoints will be analyzed using either MMRM, analysis of covariance (ANCOVA), or nonparametric inferential statistical methods and will be described in the SAP.

10.7.4. Subgroup Analyses

Efficacy analyses in the sub-groups of subjects with baseline MMSE ≤ 26 or > 26 may be performed using the MMRM method.

It is expected that approximately 80% of all subjects would be on stable doses of AChEI, approximately 90% in Mild AD and 70% in MCI. It is expected that the use of AChEI will be similar between the ALZ-801 and placebo arms. Subgroup analysis of efficacy by use of AChEI will be performed.

10.8. Biomarker Analyses

10.8.1. Cerebrospinal Fluid Biomarker Analyses

Serial CSF samples from the baseline, Week 52 and Week 78 visits will be stored and batched for analyses. Samples from multiple subjects and study sites will be analyzed in batches, at a single central laboratory, using standardized procedures and validated assays, or well performing, widely accepted CSF assays if not validated.

The CSF biomarker analyses will be performed on subjects (CSF sub-study) who have a baseline and at least one post-baseline CSF biomarker sample. The change from baseline and percent change from baseline in CSF biomarkers will be summarized by visit and treatment group. The between groups comparisons of change from baseline in each CSF biomarker will be analyzed using an MMRM model with treatment, the use of concomitant AD medications (AChEI or none), age group (50 through 65 years or > 65 years from the result of the Screening – Part 1 Visit), gender, disease severity based on MMSE at the Baseline Visit, baseline CSF biomarker level, visit, and treatment by visit interaction in the model.

10.8.2. Plasma Biomarker Analyses

Serial plasma samples from screening and each subsequent visit will be stored and batched, under GLP conditions, for analyses. Samples from multiple subjects and study sites will be analyzed at a single central laboratory using validated assays, or well performing, widely accepted plasma assays if not validated.

The plasma biomarker analyses will be performed on subjects who have a baseline and at least one post-baseline biomarker sample. The change from baseline and percent change from baseline in plasma biomarkers will be summarized by visit and treatment group. The change from baseline in each plasma biomarker will be analyzed using an MMRM model. The model will include treatment, the use of concomitant AD medications (AChEI or none), age group (50 through 65 years or > 65 years at the Screening – Part 1 Visit), gender, disease severity based on MMSE at the Baseline Visit, baseline plasma biomarker level, visit, and treatment by visit interaction in the model.

10.8.3. Imaging Biomarker Analyses

Analysis of hippocampal volume and cortical thickness will be performed using the same MMRM approach described for analysis of the primary clinical endpoint. The MMRM model will include treatment, the use of concomitant AD medications (AChEI or none), age group (50 through 65 years or > 65 years at the Screening – Part 1 Visit), gender, disease severity based on MMSE at the Baseline Visit, baseline plasma biomarker level, visit, and treatment by visit interaction. The MRI magnet strength (1.5 or 3 Tesla) will also be included as a covariate in the model.

The imaging biomarker analyses will be performed on the subjects who have a baseline and at least one post-baseline vMRI assessment.

10.9. Tests of Cognition and Function

Tests of cognition and function will be evaluated using the same approach described for the analysis of the fluid biomarkers.

10.10. Safety Analyses

Continuous safety data will be analyzed descriptively with summary statistics; and categorical safety data will be summarized using counts and percentages. The safety assessments will also include analyses of MRI findings (ARIA-E and ARIA-H) based on the central readings.

10.10.1. Adverse Events

For data summarization, AEs will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA), and reported by system organ class and preferred term.

TEAEs are defined as AEs that either started or worsened after administration of the first dose of study drug.

The number and percentage of the following types of AEs will be reported:

- TEAEs;
- TEAEs that led to study discontinuation;
- TEAEs related to study drug;
- TEAEs by maximum severity;
- SAEs; and
- SAEs related to study drug.

A listing of AEs will also be compiled.

10.10.2. Clinical Laboratory Evaluations

Clinical laboratory test results will be summarized and listed. Summary statistics for the CBL and the percentage out of range (normal reference range as established by the central laboratory) will be presented for each post-baseline time point.

Clinically notable changes in LFTs will be summarized and listed for individual study subjects. The criteria for clinically significant LFT results are as follows:

- ALT > 5 × ULN,
- AST > 5 × ULN, or
- TBL > 3 × ULN

10.10.3. MRI Safety Evaluations

The Screening – Part 2, Week 26, Week 52, and Week 78 MRIs will be assessed for occurrence of ARIA-E, ARIA-H, and macrohemorrhage by the central imaging provider (Bioclinica). Listings of these findings will be provided and summarized using descriptive statistics.

10.10.4. Vital Signs

Changes from baseline in vital sign measurements will be summarized.

Clinically notable systolic and diastolic BP while sitting will be listed for individual study subjects and summarized using descriptive statistics. Clinically notable criteria are indicated in [Table 4].

Table 4 Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic BP	> 30 mm Hg increase from baseline	> 30 mm Hg decrease from baseline
Diastolic BP	> 20 mm Hg increase from baseline	> 20 mm Hg decrease from baseline
Pulse rate	> 120 beats/min and an increase in pulse rate of ≥ 15 beats/min from baseline	< 40 beats/min and a decrease in pulse rate of ≥ 15 beats/min from baseline
Body temperature	> 39.0°C (≥ 102.2°F)	< 35.0°C (≤ 95.0°F)

BP: blood pressure

10.10.5. Electrocardiograms

All ECG intervals and durations will be reviewed for notable abnormalities according to the criteria in [Table 5]. Clinically notable abnormalities and ECG findings considered to be clinically significant will be listed. The number and percentage of study subjects who have a clinically notable ECG interval abnormality or other clinically significant ECG finding will be summarized. Assessment of clinically notable abnormalities will be based on the average of triplicate ECG readings. The criteria for QTcF are based on the upper threshold in elderly subjects [Reardon & Malik, 1996], and from other recent AD studies.

Table 5 Criteria for Clinically Notable Electrocardiogram Interval Abnormalities

Interval/Duration	High Threshold	Low Threshold
PR interval	PR interval ≥ 220 msec	PR interval ≤ 120 msec
QRS duration	QRS duration ≥ 120 msec **and** an increase in QRS duration of ≥ 20 msec from baseline	–
QT interval	QT interval > 500 msec	–
QTcF interval	QTcF interval > 500 msec and an increase in QTcF interval of ≥ 60 msec from baseline	–

QRS duration: interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization; QT interval: interval representing the time for both ventricular depolarization and repolarization to occur; QTcF: corrected QT interval using Fridericia's correction; PR interval: time from the onset of the P wave to the start of the QRS complex.

10.10.6. Physical Examination

The number and percentage of subjects with abnormal physical examination findings will be summarized. Analyses of subjects with weight loss of > 6% from baseline will be provided for subjects with weight loss without intentional dieting.

10.10.7. Neurological Examination

The number and percentage of subjects with abnormal neurological examination findings will be summarized.

10.10.8. Deaths

A listing of reported deaths, or SAEs of deaths and their narratives, will be provided.

10.11. Pharmacokinetic Analyses

10.11.1. Descriptive Pharmacokinetic Analysis

The plasma and CSF concentrations of ALZ-801, tramiprosate, and the metabolite (3-SPA) will be summarized and tabulated.

10.12. Interim Analyses

No formal interim efficacy analyses will be performed. Regular safety analyses will be performed by the DSMB and SMC, according to the schedule in their respective charters.

10.13. Measures to Minimize Bias

10.13.1. Enrollment/ Randomization/ Blinding Procedures

Subjects who meet the enrollment criteria will be randomly assigned to receive either ALZ-801 or placebo in a 1:1 ratio. The study will be conducted in a double-blinded manner. Unless otherwise specified, the Investigator and site personnel, study subjects, and Sponsor personnel will be unaware of whether subjects receive ALZ-801 or placebo until the study is formally unblinded.

During the conduct of the study, the personnel who perform the unblinded safety analysis for the DSMB will be shielded from the study team, by a firewall and other appropriate procedures. These steps are further described and documented in the DSMB charter.

10.13.2. Blinding at the Study Site and Sponsor Personnel

Study treatment group information (active drug vs placebo) will remain blinded to the subject and the study team at the study site.

During this study, Sponsor staff and designees will be blinded to treatment allocation, except as described in this section. The periodic SMC reviews will be performed in a blinded manner.

Procedures for emergency unblinding are described in Section 10.13.3. These procedures ensure that the study monitoring staff from the Clinical Research Organization, the Investigator, and other site staff do not have premature access to the study subjects' treatment assignments. Upon notification of an unblinding event, the Sponsor will assess the need for potentially removing the unblinded site personnel from the trial.

10.13.3. Breaking the Study Blind/Participant Code

In the event of a medical emergency, where knowledge of a subject's treatment assignment (ALZ-801 or placebo) must be known to facilitate appropriate medical treatment, the site investigator may break the blind to obtain immediate access to the subject's treatment assignment. The responsibility to break the treatment code in emergency situations resides solely with the investigator. Each instance of unblinding must be reported to Sponsor within 24 hours.

The Medical Monitor or designee may break the blind in the event of an SAE that requires expedited reporting to regulatory authorities. Any other requests to reveal a subject's treatment identity, apart from a medical or safety need identified by the investigator, must be approved by the Medical Monitor or designee. Upon notification of an unblinding event, the Sponsor will assess

the need for potentially removing the unblinded personnel from the trial. If a subject's treatment identity is unblinded, the subject may be withdrawn from the study and may complete the ET visit.

Details of the unblinding process to be followed are provided in the study manual(s). In the event that the treatment assignment is unblinded, Sponsor or designee will be notified immediately that the blind has been broken, and will be informed of the actual treatment assignment as required for SAE reporting or other specific reason. Other study team personnel will remain blinded unless unblinding is necessary for the safety of the subject.

The Investigator or designee is responsible for ensuring that unblinding procedures are followed, and that access is only available to the relevant staff for appropriate safety management.

11. DATA HANDLING AND RECORD KEEPING

11.1. Data Collection and Management

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

If source documents are used, they should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the eCRF, if derived from source documents, should be consistent with the source documents or the discrepancies should be explained and maintained in the participant's official study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

11.2. Access to Source Data/Case Report Forms

Every clinical site participating in this study is required to submit clinical data for each enrolled study subject via an EDC system using an eCRF. Site personnel will be trained on the EDC system before receiving access to it. The Sponsor or its designee is responsible for maintaining a record of all system users. The study subjects will not be identified by name on any study documents to be collected by the Sponsor.

All clinical information requested in this protocol will be recorded on the eCRFs provided by the Sponsor (or via other data collection methods, such as electronic laboratory data transfer). The Principal Investigator is responsible for reviewing all eCRFs, verifying them for accuracy, and approving them via an electronic signature. Copies of the completed eCRFs, saved to disk in PDF format, will be sent to the Investigator's site at the completion of the study.

The Investigator must make study data accessible to the Site Monitor (CRA), other authorized representatives of the Sponsor, Ethics Committees, and Regulatory Agency inspectors upon request. A file for each subject must be maintained that includes the signed ICF and the Investigator's copies of all source documentation related to that subject. The Investigator must

ensure the reliability and availability of source documents from which the information on the eCRF was derived.

11.3. Subject Confidentiality and Data Protection

Subject confidentiality and data protection will be handled according to applicable local laws including the General Data Protection Regulation (European Union [EU] 2016/679). Furthermore, the Investigator must ensure that each subject's privacy is protected as described below. On the eCRFs or other documents submitted to the Sponsor or its designee, subjects must be identified by no more than a Subject Identification Number. This coded information and/or samples submitted to the Sponsor may also be transferred to other countries including the US and the UK, where personal data protection laws may not be as strict as in the EU. The Sponsor and its designees are obligated to respect confidentiality and to ensure an adequate standard of personal data protection.

Documents that are not for submission to the Sponsor and/or its designee (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor (and/or its designee), representatives of regulatory agencies, and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that the above named representatives may review the subject's study-related records.

12. QUALITY MANAGEMENT

The Sponsor and designee are implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the clinical research organization will be applied.

The Sponsor or Sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, eCRFs and source documents. Direct access to these documents will be required by the auditors.

13. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

13.1. Ethical Conduct of the Study

The study will be conducted according to the protocol and in compliance with GCP, with the Declaration of Helsinki (as amended October 2013), and with other applicable regulatory requirements.

13.2. Informed Consent

At Screening – Part 1 Visit, prior to stated procedures (APOE genotyping, MMSE, demographics, medical history and prohibited medications) are performed, the site staff will obtain the signed ICF

from each participant. Complete signed ICF from subject and caregiver/study partner will be obtained prior to any other procedures at the Screening – Part 2 Visit or at the Screening – Part 1 visit if APOE4/4 status is known or confirmed using a rapid genotype test. A separate ICF will be obtained for those subjects who will participate in the CSF sub-study. The Principal Investigator and the Sponsor or designee must agree upon the format and content of the ICF before it is submitted to the IRB or IEC for approval. A written IRB/IEC-approved ICF, any other required forms to meet local or country-specific regulations must be obtained from each subject before any study-related activities are conducted.

The Investigator or Investigator's designee will explain the nature of the study to the subject, the subject's caregiver/study partner, and the subject's legally authorized representative (if applicable), and answer all questions regarding this study. Signed and dated written informed consent must be obtained from (a) the subject or (b) the subject's legally authorized representative with the subject's assent if the subject is unable or is deemed not competent, and in accordance with local regulations. The subject's caregiver/study partner must also consent to participate in the study. The Investigator must retain all original signed and personally dated ICFs (together with any subsequent IRB/IEC-approved amended versions) in the subject's file. A copy of the original signed and dated ICF (and any amendments) must be given to the subject and caregiver/study partner.

Subjects will be informed of findings from earlier or concurrent ALZ-801 clinical and nonclinical studies (including AEs) if it is determined that these could potentially affect the subject's willingness to participate or continue in the study. Depending on the nature, severity, and seriousness of these AEs, the ICF may be amended as deemed appropriate.

13.3. Regulatory Approval

The Sponsor or its designee will make the appropriate applications to the Regulatory Authority for regulatory approval of the study and, if necessary, approval to import relevant study materials. The study will not start until all required regulatory approvals have been obtained.

13.4. Ethics Committee Approval

The Investigator at the site and/or Sponsor (or designee) are responsible for obtaining IRB/IEC approval for the final protocol, ICF, advertisements to recruit subjects, and/or any other subject facing documents. Written approval of these documents must be obtained from the IRB/IEC before any subject is enrolled at a site.

The Principal Investigator and/or Sponsor (or designee) are responsible for the following interactions with the IRB/IEC:

- Obtaining IRB/IEC approval for any protocol amendments and ICF revisions before implementing the changes;
- Providing the IRB/IEC with any required information before or during the study;
- Submitting progress reports to the IRB/IEC, as required, during the conduct of the study; requesting re-review and approval of the study, as needed; providing copies of all IRB/IEC re-approvals and relevant communication to the Sponsor; and

- Notifying the IRB/IEC of all serious and unexpected AEs related to the study drug reported by the Sponsor, as required by local regulations.

13.5. Data and Safety Monitoring Board Review and Approval

The DSMB is a group of experienced AD clinical, drug safety, and statistical experts that advises the National Institute on Aging (NIA) Director, the Sponsor, and the study investigators. DSMB members serve in an independent capacity and provide their expertise and recommendations to the NIA and Sponsor, while being completely independent of the Sponsor, study Investigators, and the NIA. DSMB members will have no financial, scientific, or other conflict of interest with the trial.

The purpose of the DSMB in this study is to provide oversight of subject safety and well-being during the study conduct while maintaining strict data confidentiality. The DSMB responsibilities are to review and discuss the study data, and provide recommendations on the following:

- Overall conduct of the trial, including screening, enrollment, drop-out rates, and reasons for subject drop-out
- Aggregate and individual subject data related to safety, tolerability, and data integrity
- Recommendations to the Sponsor regarding continuation, termination or other modifications to the study, based on observed adverse effects of ALZ-801
- Evaluation of emergent data from other ALZ-801 studies or other AD clinical trials, that may impact subject safety, change the benefit risk profile of ALZ-801, or alter the ethics of the trial design
- Protection of subjects' safety and well-being throughout the study
- Additional recommendations, as appropriate, if unexpected findings arise
- Advice to the NIA leadership on any aspect of the study

13.6. Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of the Sponsor and/or designee and the applicable regulatory authorities, as appropriate. The IRB/IEC must be informed of all amendments and give approval for any amendments likely to affect the safety of the study subjects or the conduct of the study. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor and/or designee.

The study may be terminated in accordance with the terms of the Clinical Trial Agreement (CTA). The Investigator should notify the IRB/IEC in writing of the study's completion or ET and send a copy of the notification to the Sponsor and/or designee. Regulatory notifications of study termination or completion will be filed in accordance with applicable local regulations.

13.7. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (http://private.ich.org/LOB/media/MEDIA482.pdf) The study will conform to ICH GCP Guidelines and all applicable FDA, Health Canada, EU, and national laws and regulations.

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator and/or Sponsor (designee).

13.8. Finance, Insurance, and Indemnity

Finance, insurance, and indemnity terms are delineated in the CTA.

14. PUBLICATION PLAN

Publication rights are delineated in the CTA.

15. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence by the Sponsor or pharmaceutical industry is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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17. APPENDIX

Appendix 1 Key Personnel

Function	Personnel and Contact Information
24-hour Contact for Serious Adverse Events (SAEs) See [Section 8.4.2 Collecting, Reporting, and Recording Serious Adverse Events]	**Please fax or email the SAEs to:** [redacted] Department: Pharmacovigilance and Safety Services [redacted]
Medical Monitor/Study Physician	[redacted]
Backup Medical Monitor/Study Physician	[redacted]
Sponsor Study Physician and Medical Officer	[redacted] Chief Medical Officer 111 Speen Street, Suite 306 Framingham, MA 01701 USA [redacted]

Appendix 2 Schedule of Assessments

	Screening*			Double-Blind Treatment										
Visit (V)	**V 1a**	**V 1b**	**V 2**	**V 3 Phone**	**V 4**	**V 5**	**V 6 Phone**	**V 7**	**V 8**	**V 9**	**V 10**	**V 11 EOT**	**ET**	**Safety FU EOS**
Visit Time	**Scr – Part 1**	**Scr – Part 2**	**Bsl Day1**	**W 2 Day15**	**W 6 Day43**	**W 13 Day92**	**W 20 Day141**	**W 26 Day183**	**W 39 Day274**	**W 52 Day365**	**W65 Day456**	**W 78 Day547**	**TBD**	**W 82 Day574**
Window	**Up to -13 weeks**	**–**	**–**	**± 2 d**	**± 7 d**	**± 14 d**	**± 2 d**	**± 14 d**	**± 14 d**	**± 14 d**	**± 14 d**	**± 14 d**	**–**	**± 7 d**
Informed consent/ caregiver/study partner consent[1]	X	X												
MMSE Score	X		X			X		X	X	X	X	X	X	
Prohibited medications	X													
Demographics, medical history	X													
APOE testing	X													
Vital signs[2]		X	X		X	X		X	X	X	X	X	X	X
Physical examination		X	X		X	X		X	X	X	X	X	X	X
Neurological examination		X						X		X		X	X	X
Height		X												
Weight		X	X		X	X		X	X	X	X	X	X	X
Prior/concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
AD diagnostic criteria		X												
RBANS		X												
Evidence of progressive memory loss over the last 12 months		X												
12-Lead ECG[3]		X			X	X		X		X		X	X	
Future potential genomic testing		X												

	Screening*			Double-Blind Treatment										
Visit (V)	**V 1a**	**V 1b**	**V 2**	**V 3 Phone**	**V 4**	**V 5**	**V 6 Phone**	**V 7**	**V 8**	**V 9**	**V 10**	**V 11 EOT**	**ET**	**Safety FU EOS**
Visit Time	**Scr – Part 1**	**Scr – Part 2**	**Bsl Day1**	**W 2 Day15**	**W 6 Day43**	**W 13 Day92**	**W 20 Day141**	**W 26 Day183**	**W 39 Day274**	**W 52 Day365**	**W65 Day456**	**W 78 Day547**	**TBD**	**W 82 Day574**
Window	**Up to -13 weeks**	**–**	**–**	**± 2 d**	**± 7 d**	**± 14 d**	**± 2 d**	**± 14 d**	**± 14 d**	**± 14 d**	**± 14 d**	**± 14 d**	**–**	**± 7 d**
Safety lab tests[4]		X			X	X		X	X	X	X	X	X	
Serum FSH/hCG test[5]		X												
Immunology (HIV, Hep B S Ag, Hep C Ab, HCV RNA if applicable)		X												
Urinalysis		X			X	X		X		X		X	X	
Urine Pregnancy test[6]			X		X	X		X	X	X	X	X	X	
Urine drug screen		X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI[7]		X						X		X		X	X	
Inclusion/ exclusion criteria			X											
Randomization			X											
ADAS-Cog			X			X		X		X		X	X	
A-IADL			X					X		X		X	X	
CDR[8]		X						X		X		X	X	
DAD			X					X		X		X	X	
NPI			X					X		X		X	X	
QoL-AD			X							X		X	X	
RUD Lite			X							X		X	X	
C-SSRS[9]		X	X		X	X		X	X	X	X	X	X	X
CSF sampling[10]			X							X		X	X	
Plasma biomarkers			X		X	X		X	X	X	X	X	X	
PK sample collection[11]			X		X	X		X	X	X	X	X	X	

	Screening*			Double-Blind Treatment										
Visit (V)	**V 1a**	**V 1b**	**V 2**	**V 3 Phone**	**V 4**	**V 5**	**V 6 Phone**	**V 7**	**V 8**	**V 9**	**V 10**	**V 11 EOT**	**ET**	**Safety FU EOS**
Visit Time	**Scr – Part 1**	**Scr – Part 2**	**Bsl Day1**	**W 2 Day15**	**W 6 Day43**	**W 13 Day92**	**W 20 Day141**	**W 26 Day183**	**W 39 Day274**	**W 52 Day365**	**W65 Day456**	**W 78 Day547**	**TBD**	**W 82 Day574**
Window	**Up to -13 weeks**	**_**	**_**	**± 2 d**	**± 7 d**	**± 14 d**	**± 2 d**	**± 14 d**	**± 14 d**	**± 14 d**	**± 14 d**	**± 14 d**	**_**	**± 7 d**
Time of last dose prior to clinic visit					X	X		X	X	X	X	X	X	
Study drug return, accountability, compliance					X	X		X	X	X	X	X	X	
Study drug dosing on site[12]			X		X	X		X	X	X	X	X		
Dispense study drug[13]			X		X	X		X	X	X	X			

ADAS-Cog: Alzheimer's Disease Assessment Scale – cognitive subscale; A-IADL: Amsterdam Instrumental Activities of Daily Living; APOE: apolipoprotein E; BP: blood pressure; Bsl: baseline; CDR: Clinical Dementia Rating; CSF: cerebrospinal fluid; C-SSRS: Columbia-Suicide Severity Rating Scale; CT: computed tomography; d: Day; DAD: Disability Assessment for Dementia; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; ET: early termination; FSH: follicle-stimulating hormone; FU: Follow-up; hCG: human chorionic gonadotropin; HCV RNA: hepatitis C virus RNA; Hep B S Ag: hepatitis B surface antigen; Hep C Ab: hepatitis C antibody; HIV: human immunodeficiency virus; LP: lumbar puncture; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; NPI: Neuropsychiatric Inventory; PK: pharmacokinetics; QoL-AD: Quality of Life in Alzheimer's Disease; QTc: corrected QT (interval); Scr: Screen; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RUD Lite: Resource Utilization in Dementia Lite version; TBD: to be determined; V: visit; W: week.

* Previous evidence of APOE4/4 status may be used as a reference and allow subjects to combine Screening – Par 1 Visit and Screening – Part 2 Visit together at the same day if the site and subject prefer. Screening procedures may be conducted over several visits during the Screening period provided that the results are available to evaluate inclusion and exclusion criteria before randomization.

1. Informed consent at Screening – Part 1 Visit is for APOE genotyping, MMSE, demographics, medical history and prohibited medications. Complete consent from subject and caregiver/study partner at the Screening – Part 2 Visit or at the Screening – Part 1 Visit if APOE4/4 status is known or confirmed using a rapid genotype test.
2. Vital sign measurements (BP, pulse, respiratory rate, and body temperature) will occur prior to dosing, LP, and blood draw, where applicable. BP and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person, using an inflatable cuff and calibrated manometer. After last blood collections, subjects will be observed for approximately 15 minutes. BP and pulse while sitting will be measured and documented at the end of this observation period.
3. ECGs should be obtained after the subject has rested quietly in the supine position for at least 5 minutes. Triplicate ECG will be performed at screening, Week 6, and Week 13. Triplicate ECG at Week 26, Week 52, Week 78, and ET will be performed only if QTc prolongation observed in current and prior visits.
4. Lab tests include clinical chemistry, hematology, and coagulation tests, and will be done after ADAS-Cog and CDR-SB assessments.

5. Serum FSH levels will be measured only for female subjects of non-childbearing potential. Serum hCG levels will be measured only for female subjects of childbearing potential.
6. Urine pregnancy tests will be conducted only for female subjects of childbearing potential.
7. For those who cannot undergo MRI, CT is acceptable at Screening but requires prior approval by Medical Monitor. These subjects will not be scheduled for further CT imaging and will not contribute to the assessment of the volumetric imaging biomarkers. Note: CT is not allowed for subjects of sites at Germany.
8. At screening, CDR global score and memory box score are calculated for screening purposes; the sum of boxes score is recorded at subsequent visits.
9. C-SSRS: B/S = baseline/screening version, SLV = since last visit version.
10. This CSF sub-study intends to enroll 60 subjects per treatment group. For each subject, LP will be performed within the same 2-hour window on each of the 3 visits regardless of dosing time and other assessments. In other words, for any two of the three CSF collections, the maximal time difference, in terms of the time of day, is within 2 hours from each other. Time of CSF collection (not time of preparation) will be recorded.
11. Plasma PK samples will be collected at pre-dose at each clinic visit. Additional, a PK sample at ≥ 1 hour post-dose during clinic visit will be collected at Week 65.
12. The times of study drug administration when taken at the study site will be recorded.
13. Last study drug administration will occur on the morning of the Week 78 visit. One dose is administered at the site during clinic visits; the evening dose is skipped on clinic visit days.